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ARNOLD S RELMAN MD EDITOR
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The Western Journal of Medicine

VOLUME 141 • NUMBER 1 JULY 1984

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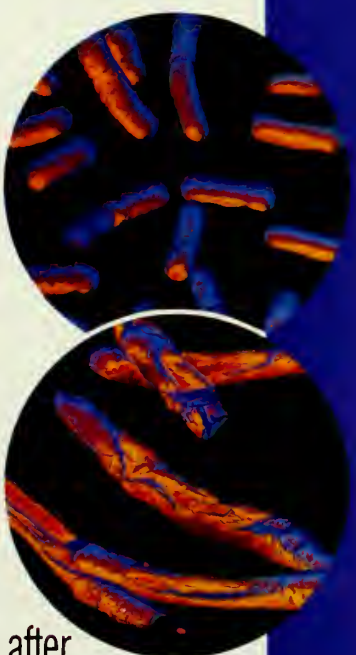
before

Color-enhanced scanning electron micrograph shows *E. coli* 736 culture growing on Adams and Roe agar.



after

E. coli 736 culture after 24-hour incubation with Bactrim (trimethoprim and sulfamethoxazole/Roche) at 5×MIC. Note distorted shape of destroyed bacteria.

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A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. This presentation was the 14th Annual Paul Aggeler Memorial Lecture, October 18, 1983, San Francisco General Hospital Medical Center.

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Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System —** Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory —** Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal —** Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous —** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System —** reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal —** mesenteric arterial thrombosis; ischemic colitis. **Hematologic —** agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic —** fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous —** reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

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Please allow 4-6 weeks for delivery.

Reference: 1. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: 1984 Report. Arch Intern Med 144(5): 1045-1057, 1984.

Please see adjacent page of this advertisement for brief summary.

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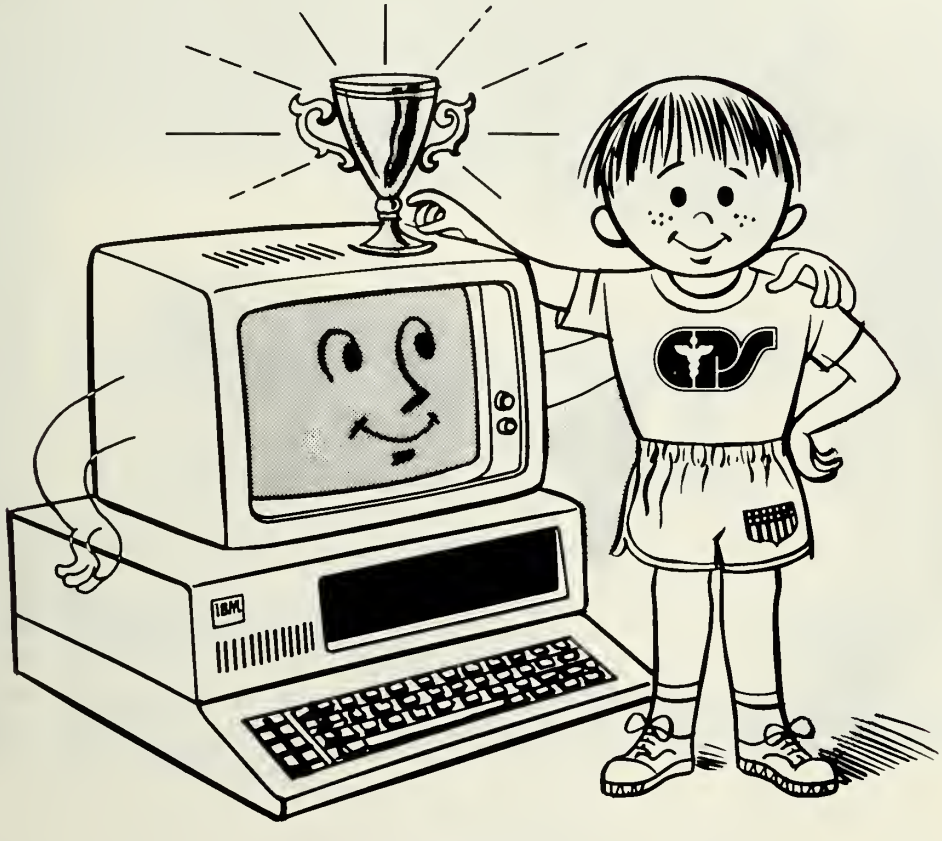

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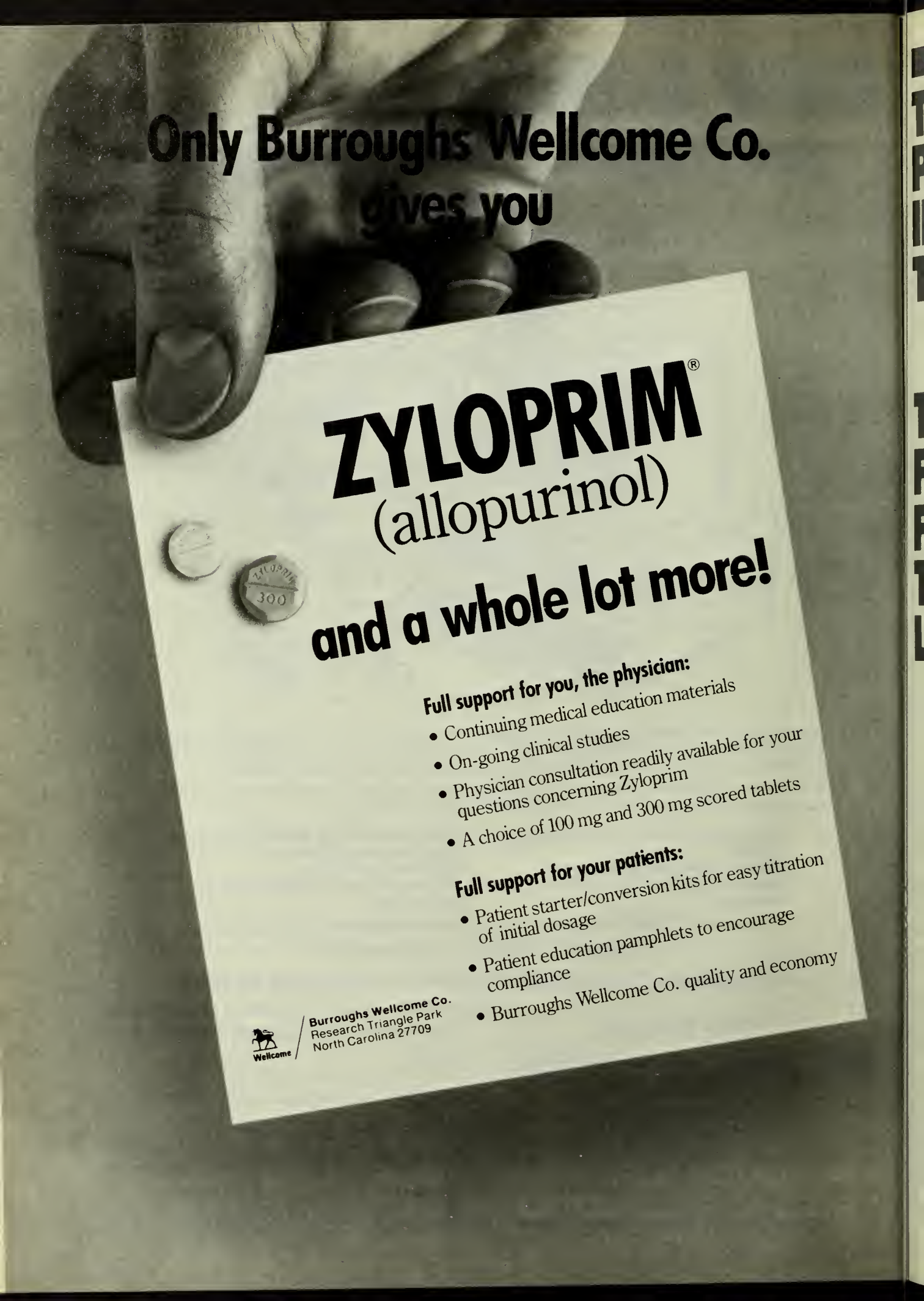
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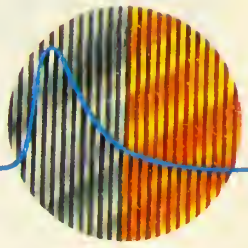
Halcion® 0.25 mg Tablets

triazolam (IV)

Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion
triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

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Halcion Tablets
triazolam (IV)

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 198

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42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

CARDIZEM®
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THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

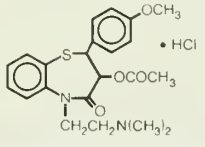
2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 2D mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 2D%. In a study involving single oral doses of 3DD mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 5D% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 8D% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 7D% to 8D% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 3D to 6D minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 2D% of the parent drug and is 25% to 5D% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 5D to 2DD ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 12D-mg dose gave blood levels three times that of the 6D-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 9D mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 2D%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 2D times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 6D-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 3DD mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE ANO AOMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 18D to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

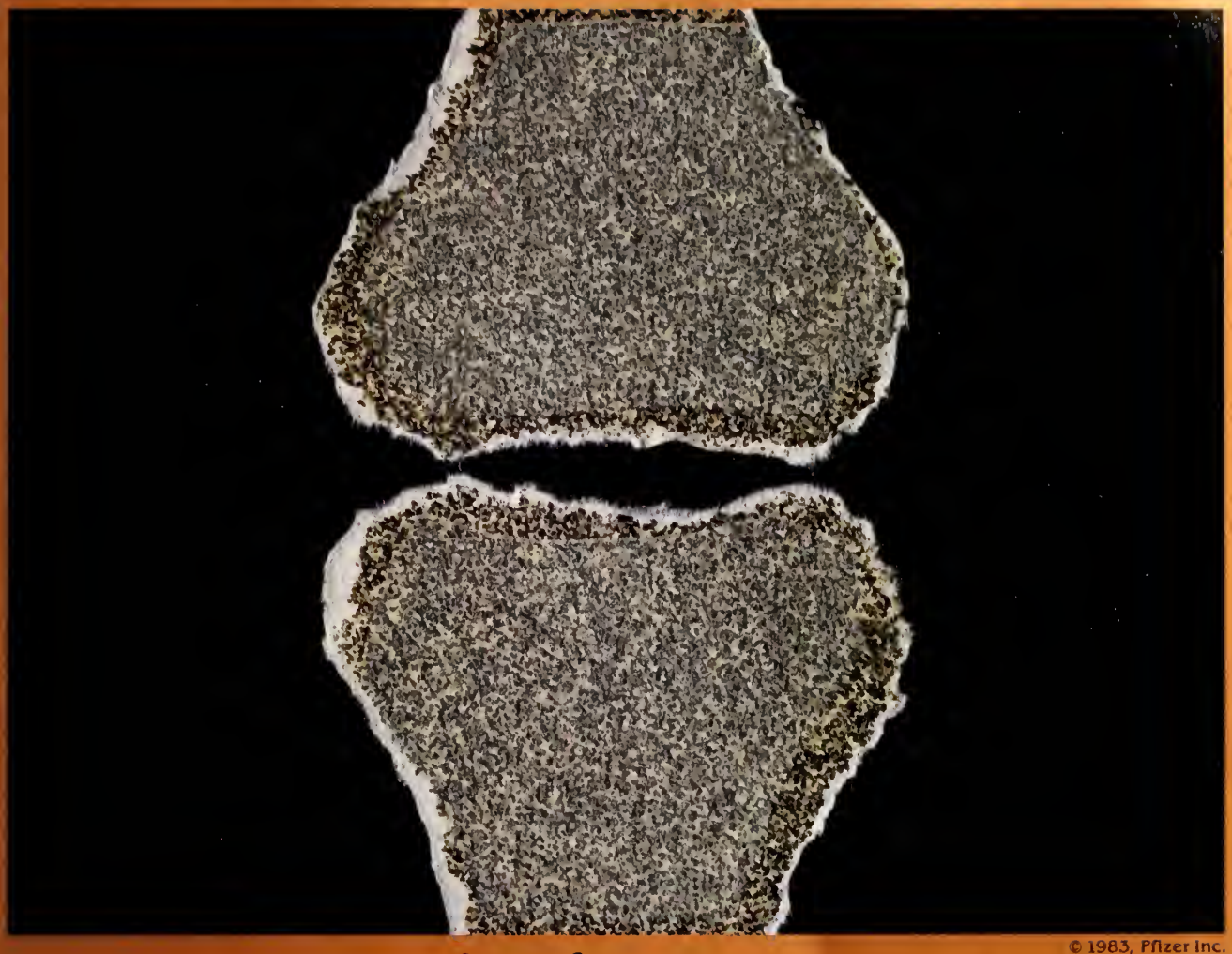
HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC D088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 1DD (NDC 0088-1772-49). Each yellow tablet is engraved with MARIDN on one side and 1772 on the other.

Issued 4/1/84

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137



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This is how an arthritis patient's joints often feel.

You can help these patients feel better with one-a-day FELDENE (piroxicam).
For good reasons:

- it's effective—proven relief of the pain and inflammation of rheumatoid arthritis and osteoarthritis in millions of patients, in 80 countries all around the world.
- it's efficient—once daily, 20-mg dose provides round-the-clock relief, improves compliance and remains effective during long-term therapy, maintaining 24-hour therapeutic blood levels once steady state is reached in 7 to 12 days.
- it's preferred—in an open multi-center study, the antiarthritic preferred by physicians for their patients was FELDENE.[1]

Feldene® (PIROXICAM) 20 mg capsules

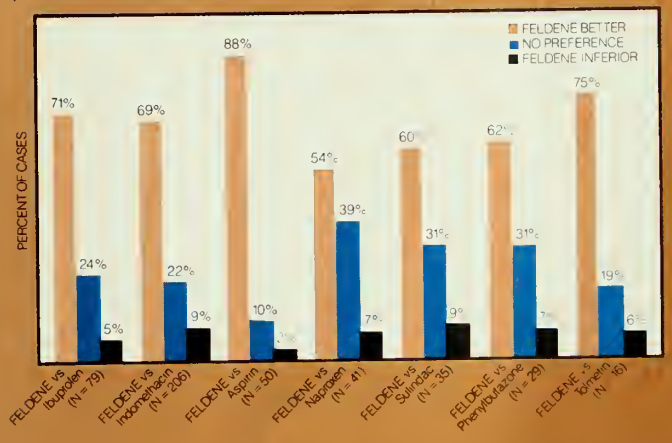
ONE-A-DAY

Please see a brief summary of FELDENE (piroxicam) prescribing information on the following page.

Feldene®
(PIROXICAM) 20 mg capsules

Rated better by physicians in an open multicenter trial

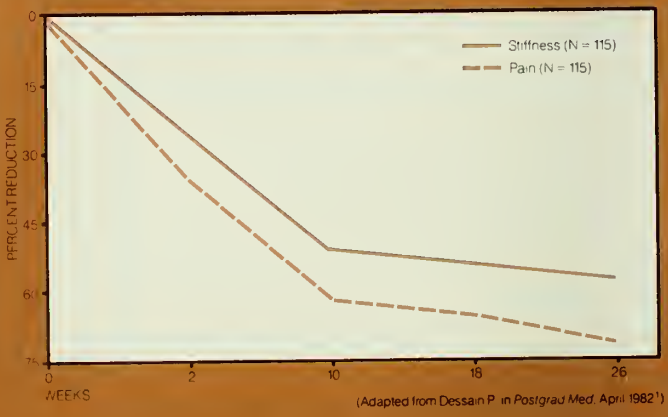
INVESTIGATORS' COMPARATIVE GLOBAL EVALUATIONS
(Physicians rated Feldene therapy as "better than," "equal to," or "inferior to" previous therapy based on global evaluations of patients' overall response.)



(Adapted from Dessain P. in *Postgrad Med.* April 1982[1])

Investigators' global comparisons of Feldene and previous medications in multicenter open trials by 156 physicians in 749 osteoarthritis patients who had been on previous drug therapy. The above chart includes only those drugs available in the U.S. Average FELDENE dose was 20 mg/day.

REDUCTION IN PAIN AND STIFFNESS
Patients with osteoarthritis evaluated over 6 months on Feldene (mean dose of 20 mg/day) therapy showed dramatic reduction in pain and stiffness.



(Adapted from Dessain P. in *Postgrad Med.* April 1982[1])

Multicenter long-term follow-up of 154 patients who had shown adequate response to piroxicam in short-term trials. 115 patients for whom complete data were available at every assessment visit through 26 weeks.

Reference

1. Dessain P. Efficacy and toleration of piroxicam in general practice. A multicenter study of osteoarthritis. *Postgrad Med* (special report) 76–81, April 1982.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia.

Dermatologic: pruritus, rash.

Central Nervous System: dizziness, somnolence, vertigo.

Urogenital: BUN and creatinine elevations (see PRECAUTIONS).

Body as a Whole: headache, malaise.

Special Senses: tinnitus.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

* Reactions occurring in 3% to 9% of patients treated with FELDENE (piroxicam).

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions.

Central Nervous System: depression, insomnia, nervousness.

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS).

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS).

Special Senses: swollen eyes, blurred vision, eye irritations.

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina.

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease.

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS).

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis.

Dermatologic: onycholysis, loss of hair.

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias.

Urogenital System: dysuria.

Body as a Whole: weakness.

Cardiovascular/Respiratory: palpitations, dyspnea.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis. It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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Pfizer LABORATORIES DIVISION
PFIZER INC

A Near-Spotless Record.

Other OCs claim it. We show it.[1*]

In clinical trials, Lo/Ovral was practically perfect in holding spotting and breakthrough bleeding to a minimum.†

	SPOTTING	BREAKTHROUGH BLEEDING
Cycle 1	10.6%	8.8%
Cycle 3	6.3%	3.3%
Total Cycles‡	4.2%	2.9%

Lo/Ovral® offers less breakthrough bleeding and spotting, along with high contraceptive efficacy, at a low dose—just 30 mcg ethinyl estradiol and 0.3 mg norgestrel.

LOW DOSE

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth.

1 Dickey RP. Managing Contraceptive Pill Patients, 3rd ed., Durant, Oklahoma, Creative Informatics, Inc., 1983

*Rates are derived from separate studies from different investigators in several population groups and cannot be compared precisely

†Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives

‡Data on file for 22,489 total cycles, Wyeth Laboratories See important information on following page

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions.

1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (see Warning No. 5)
8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF OOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

PERSISTENCE OF RISK OF VASCULAR DISORDERS—Findings from one study in Britain involving cerebrovascular disease and another in the U.S. concerning MI suggest an increased risk of these conditions in users of OC's persists after discontinuation of the OC's. In the British study, risk of cerebrovascular disease remained elevated in former OC users for at least 6 years after discontinuation. In the U.S. study, increased risk of MI persisted for at least 9 years in women 40 to 49 years old who had used OC's for 5 or more years. Findings in both studies require confirmation since they are inconsistent with other published information.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind.

In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions GENERAL. 1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests.

As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient See Patient Package Labeling.

Drug Interactions Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies.

There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema, chloasma or melasma which may persist, breast changes (tenderness, enlargement, and secretion), change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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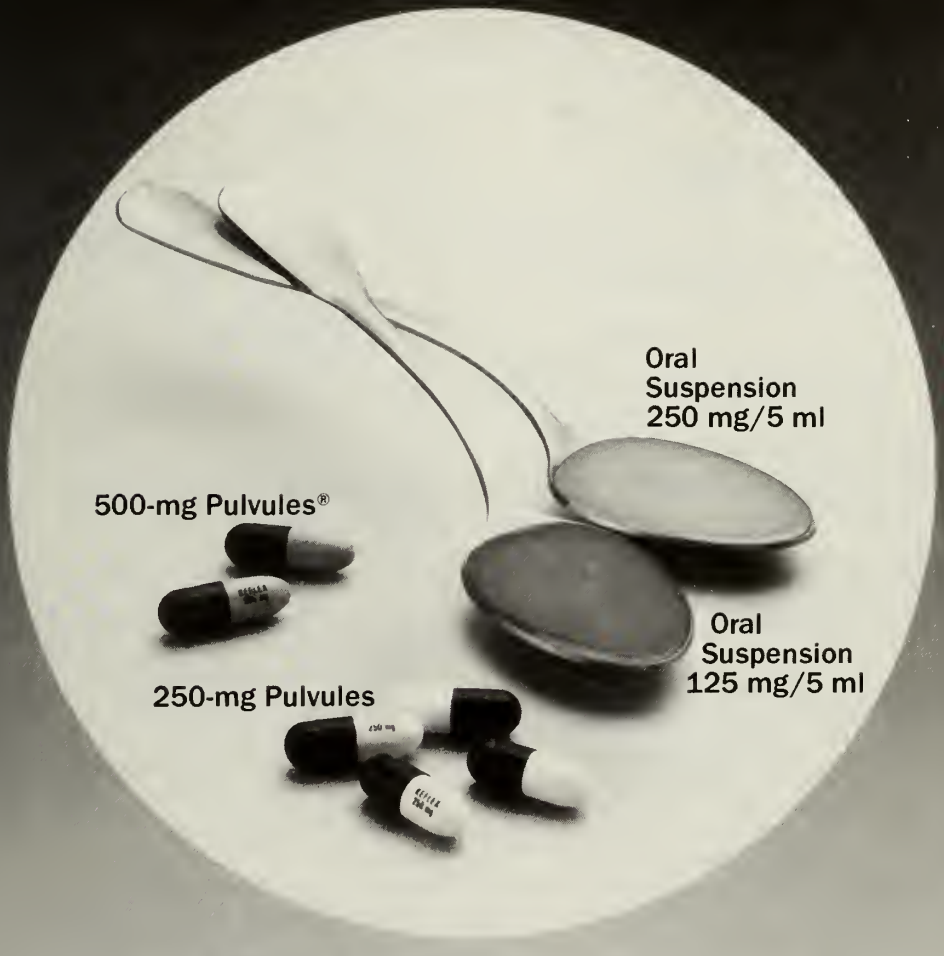

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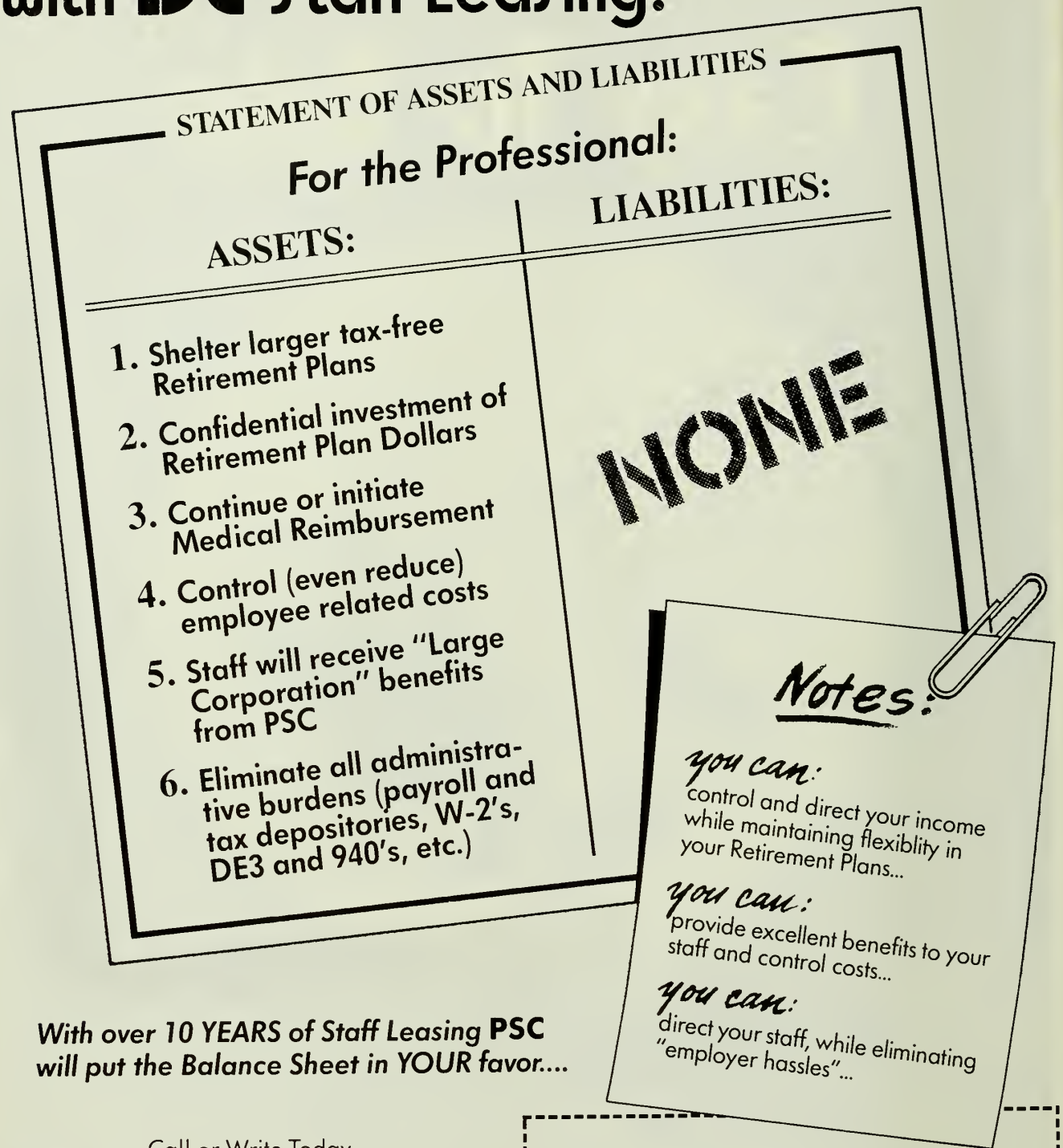
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ALLERGY AND IMMUNOLOGY

October 4-6—**Allergy/Immunology.** UCSF. Thursday-Saturday.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Monday-Thursday. $375.

October 20—**Allergy Update—A Clinical Symposium.** Allergy Foundation of Northern California, Allergy Association of Northern California and the California Society of Allergy at Holiday Inn Union Square, San Francisco. Saturday. Contact: Dr. Chester Trossman, 500 E. Remington Dr., Sunnyvale 94087. (408) 730-0812.

October 24-28—**American Association for Clinical Immunology and Allergy Meeting** at San Diego. Wednesday-Sunday. Contact: Howard S. Silber, Exec. Dir., PO Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

October 25-28—**Allergy, Immunology and Infectious Disease.** Symposium Maui, Inc. and Hawaii Chapter American Academy of Family Physicians at Maui Marriott, Kaanapali, Maui. Thursday-Sunday. 18 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., PO Box 10185, Lahaina, Maui, HI 96761. (808) 661-8032.

ANESTHESIOLOGY

August 17-21—**Clinical Neuroanesthesia Conference.** UCSD at InterContinental Hotel, San Diego. Friday-Tuesday. 22 hrs.

August 19-25—**11th Hawaiian Seminar: Clinical Anesthesiology.** California Society of Anesthesiologists at Maui Surf Hotel, Maui. Sunday-Saturday. $350. Contact: Educational Programs Division, California Society of Anesthesiologists, 100 So. Ellsworth Ave., Ste. 806, San Mateo, CA 94401. (415) 348-1407.

September 8-9—**Case Conference.** High Sierra Hotel at South Shore, Lake Tahoe. Saturday-Sunday. $145. Contact: Educational Programs Division, California Society of Anesthesiolo-

(Continued on Page 31)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward. Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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(PROPRANOLOL HCl) LONG ACTING CAPSULES

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DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used for the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirements of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length and diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by decreased frequency of anginal and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in cerebral vessels in man.

Beta receptor blockade can be useful in conditions in which because of atherosclerotic or functional changes, sympathetic activity is detrimental. In these situations, full therapeutic also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in rats and mice employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity or drug-related tumorigenic effects at any of the dosage levels. Reproduction studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 6 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss; emotional lability; slightly clouded sensorium; and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

Just once each day for initial therapy

(Continued from Page 27)

gists, 100 So. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

September 28-30—**Anesthesia Practice 1984.** Anesthesiology Education Foundation at Monterey. Friday-Sunday. 10½ hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles 90024.

October 20—**Annual Anesthesiology Symposium.** Kaiser Permanente Southern California Medical Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

CANCER

October 18-20—**8th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. $300. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

CARDIOLOGY

August 12-17—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

August 17-19—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 24-26—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress and Holter) and Cardiac Resuscitation.** International Medical Education Corporation at Monterey. Friday-Sunday. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 7-9—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Hyatt Islandia, San Diego. Friday-Sunday. Contact: Beverly Jacobsen (800) 525-8651.

September 14-16—**ECG Interpretation, Arrhythmia, and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 15-22—**Hawaiian Echocardiography Course.** Institute for Medical Studies at Hawaiian Islands. One week. 20 hrs. $295. Contact: IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

September 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Meridien Hotel, San Francisco. Thursday-Saturday.

October 7-10—**Cardiology Course.** UCSF at Yosemite. Sunday-Wednesday.

October 11-13—**Cardiology Update—1984.** ACC at Hyatt Del Monte Hotel, Monterey. Thursday-Saturday.

October 15-19—**Pulmonary Medicine Review 1984.** USC. Monday-Friday. $450.

October 26-28—**ECG Interpretation, Arrythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at San Francisco. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

EMERGENCY MEDICINE

July 16-20—**Postgraduate Institute for Emergency Physicians.** UCSD. Monday-Friday. 33 hrs.

July 30-31—**Advanced Cardiac Life Support.** Emergency Care Education Center, Emergency Department Physicians, and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina Del Rey 90291. (213) 822-1312.

August 3-5—**Whitewater Raft Conference: Trauma Evaluation and Treatment.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center,

(Continued on Page 33)

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE ALCOHOLIC PATIENT: DIAGNOSIS AND MANAGEMENT—Morris E. Chafetz, MD. Medical Economics Books, Box 157, Florence, KY 41042, 1983. 221 pages, $22.50* plus $1.50 handling charge. *Note: Prices are subject to change without notice. Payment should accompany orders.

THE ANTHROPOLOGY OF MEDICINE—From Culture to Method—Lola Romanucci-Ross, Daniel E. Moerman, Laurence R. Tancredi, MD, and contributors. Bergin & Garvey Publishers, Inc, 670 Amherst Road, South Hadley, MA 01075, 1983. 400 pages, $34.95 (cloth); $16.95 (paperback).

THE CLINICAL NEUROSCIENCES—Section IV, NEURORADIOLOGY—Editor: Roger N. Rosenberg, MD, Professor of Neurology and Physiology, Chairman, Dept of Neurology, University of Texas Health Science Center at Dallas, Southwestern Medical School, Chief, Neurological Services, Parkland Hospital and Children's Medical Center, Dallas; Associate Editor: E. Ralph Heinz, MD, Professor of Radiology (Neuroradiology), Duke University School of Medicine, Durham, NC; with 19 contributors. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 968 pages, $150.00.

CURRENT MEDICAL DIAGNOSIS & TREATMENT—1984—Edited by Marcus A. Krupp, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine, and Director of Research Institute, Palo Alto Medical Foundation, and Milton J. Chatton, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine; Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, and Research Associate, Palo Alto Medical Foundation, Palo Alto, California. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 1,114 pages, $26.00 (softbound).

THE DOCTOR'S COMPUTER HANDBOOK—Peter J. Fell, MD, general practitioner in Deddington, Oxford, England; and William D. Skees, President of Skees Associates, Inc, Alexandria, Virginia, an automation consulting firm. Lifetime Learning Publications, Ten Davis Drive, Belmont, CA 94002, 1984. 268 pages, $27.50.

DRUGS USED WITH NEONATES AND DURING PREGNANCY—Second Edition—Ina Lee Stile, PharmD; Thomas Hegyi, MD, and I. Mark Hiatt, MD. Medical Economics Books, Oradell, NJ 07649, 1984. 146 pages, $10.95 (paperback).

FUNDAMENTALS OF INFECTION CONTROL: AN IN-SERVICE ORIENTATION PROGRAM—Editor and Principal Author: Charles P. Craig, MD, Professor of Medicine, and Director, Division of Infectious and Tropical Diseases, University of South Florida College of Medicine, Tampa. Medical Economics Books, Box 157, Florence, KY 41042, 1983. 286 pages, $17.95 plus $1.50 handling charge.

INSURANCE STRATEGIES FOR PHYSICIANS, 1983—Phillips Huston. Medical Economics Books, Box 157, Florence KY 41042, 1983. 160 pages, $22.50,* plus a $1.50 handling charge. *Prices are subject to change without notice.

KEY FACTS IN PULMONARY DISEASE—Edited by Om P. Sharma, MD, Professor of Medicine, University of Southern California School of Medicine, Physician, Los Angeles County-USC Medical Center, Los Angeles; and Oscar J. Balchum, MD, PhD, Hastings Professor of Medicine, University of Southern California School of Medicine, Chief Physician, Pulmonary Disease Section, Los Angeles County-USC Medical Center, Los Angeles. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1983. 598 pages, $37.50 (softbound).

MEDICINE: THE STATE OF THE ART—Charles Mangel and Allen B. Weisse, MD. Doubleday & Company, Inc, 245 Park Ave, New York, NY 10167, 1984. 304 pages, $15.95.

MUSCLE PATHOLOGY—Vol. 3 in CONTEMPORARY ISSUES IN SURGICAL PATHOLOGY—Edited by Reid R. Heffner, Jr, MD, Director, Department of Pathology, Erie County Medical Center, and Professor of Pathology, State University of New York at Buffalo School of Medicine, Buffalo. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 230 pages, $45.00.

PRIMARY CARE RESEARCH—Encounter Records and the Denominator Problem—Edited by S. James Kilpatrick, Jr, and Russell M. Boyle. Praeger Publishers, CBS Educational and Professional Publishing, a Division of CBS Inc, 521 Fifth Avenue, New York, NY 10175, 1984. 156 pages, $27.95.

PRINCIPLES AND PRACTICE OF MEDICAL GENETICS—2 Volumes—Edited by Alan E. H. Emery, MD, PhD, DSc, FRCP(E), FRS(E), Professor and Chairman, University Department of Human Genetics, Western General Hospital, Edinburgh, and David L. Rimoin, MD, PhD, Professor of Pediatrics and Medicine, UCLA School of Medicine, and Chief, Division of Medical Genetics, Harbor-UCLA Medical Center, Los Angeles. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1983. 1,502 pages, $150.00.

RECENT ADVANCES IN DERMATOLOGY—No. 6—Edited by Arthur J. Rook, MA, MD, FRCP, Consultant Dermatologist, Addenbrooke's Hospital, Cambridge, United Kingdom, and Howard I. Maibach, MD, Professor of Dermatology, University of California, San Francisco, School of Medicine. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 276 pages, $40.00.

RECENT ADVANCES IN DIABETES—No. 1—Edited by Malcolm Nattrass, MB, ChB, PhD, MRCP, Consultant Physician, The General Hospital, and Senior Clinical Lecturer, The University of Birmingham, Birmingham, United Kingdom, and Julio V. Santiago, MD, Professor of Pediatrics and Medicine and Associate Director, Diabetes Research and Training Center, Washington University School of Medicine, St Louis. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 254 pages, $35.00 (softbound).

RECENT ADVANCES IN ENDOCRINOLOGY AND METABOLISM—NUMBER TWO—Edited by J. L. H. O'Riordan, DM(Oxon), FRCP, Reader in Metabolic Medicine and Deputy Director of The Department of Medicine, The Middlesex Hospital Medical School, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 327 pages, $45.00 (softbound).

RECENT ADVANCES IN HEPATOLOGY—No. 1—Edited by Howard C. Thomas, MB, BS, BSc, PhD, FRCP, Reader in Medicine and Consultant Physician, Royal Free Hospital and Medical School, London, and Roderick N. M. MacSween, BSc, MD, FRCP(E), FRCP(G), FRCPath, Titular Professor and Honorary Consultant Pathologist, University Department of Pathology, Western Infirmary, Glasgow, United Kingdom. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 256 pages, $45.00.

RECENT ADVANCES IN RESPIRATORY MEDICINE—No. 3—Edited by David C. Flenley, PhD, FRCP, FRCPE, Professor of Respiratory Medicine, University of Edinburgh, and Thomas L. Petty, MD, Professor of Medicine and Anesthesiology, and Head, Division of Pulmonary Sciences, University of Colorado Health Sciences Center, Denver. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1984. 287 pages, $37.50, (paperback).

RECENT ADVANCES IN RHEUMATOLOGY—No. 3—Edited by W. Carson Dick, MD, FRCP, Reader in Rheumatology, University of Newcastle, and Honorary Consultant Physician at the Royal Victoria Infirmary and The Freeman Hospital, Newcastle upon Tyne, and J. M. H. Moll, BSc, DM, PhD, FRCP, Consultant Physician in Rheumatology and Head, Sheffield Centre for Rheumatic Diseases, Nether Edge Hospital, and Honorary Clinical Lecturer in Rheumatic Diseases, University of Sheffield, United Kingdom. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 233 pages, $44.00.

REGULATORY PEPTIDES OF GUT AND BRAIN—British Medical Bulletin, Volume 38, No. 3—Edited by R. A. Gregory, CBE, FRS. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1982. 94 pages, $19.50.

RESPIRATORY MONITORING IN INTENSIVE CARE—Volume 4 in Clinics in Critical Care Medicine Series—Edited by Alastair A. Spence, MD, FFARCS, MRCP. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1982. 162 pages, $28.00.

REVIEW OF MEDICAL PHYSIOLOGY—11th Edition—William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 643 pages, $20.00.

SAUNDERS DICTIONARY & ENCYCLOPEDIA OF LABORATORY MEDICINE AND TECHNOLOGY—Editor: James L. Bennington, MD, Chairman, Department of Anatomic Pathology and Clinical Laboratories, Children's Hospital of San Francisco; with Associate Editors. WB Saunders Company, West Washington Square, Philadelphia, PA 19105, 1984. 1,674 pages, $45.00.

SCANNING ELECTRON MICROSCOPY OF MEDICALLY IMPORTANT PARASITES—Viqar Zaman, DSc, MBBS, D TM&H, FRCPath, Professor and Chairman, Department of Microbiology, Faculty of Medicine, National University of Singapore. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 115 pages, $32.50.

THE SEVERELY INJURED LIMB—Christopher E. Ackroyd, MA, MB, BChir, FRCS, Consultant Orthopaedic Surgeon, Southmead General Hospital, Bristol, and Brian T. O'Connor, MS, MChOrth, FRCS, FRACS, Robert Jones Professor of Orthopaedics, Robert Jones and Agnes Hunt Hospital, Oswestry, Shropshire, England, and Pieter F. de Bruyn, FCRS, Consultant Orthopaedic Surgeon, Tiel Hospital, Tiel, The Netherlands. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 258 pages, $44.00.

SNAKE VENOM POISONING—Findlay E. Russell, MD, PhD, Professor of Pharmacology and Toxicology, University of Arizona, Tucson; Adjunct Professor of Neurology, University of Southern California, Los Angeles; and Adjunct Professor of Neuropharmacology, Loma Linda University, Loma Linda, California. Scholium International, Inc., 265 Great Neck Rd., Great Neck, NY 11021, 1983. 562 pages, $57.50.

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Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 18—**Emergency Medicine Oral Boards Part II.** Highland General Hospital at Hyatt Regency Hotel, Oakland. Saturday. $495. Contact: Robert H. Dailey. (415) 534-8055, Ext. 207.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** American College of Obstetrics and Gynecology at Hotel del Coronado, Coronado. Wednesday-Friday. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 24-26—**Wilderness Emergency Care—Mt. Shasta Summit Expedition.** Mercy Medical Center, Redding at Mt. Shasta. Friday-Sunday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 27-31—**Topics in Emergency Medicine.** UCSF at San Francisco. Monday-Friday. $425.

September 1-3—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Klamath River. Saturday-Monday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

September 6-7—**Burns: Emergency and Acute Care.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Friday.

September 17-21—**Postgraduate Institute for E.R. Physicians, Symposium I.** UCSD at InterContinental Hotel, San Diego. Monday-Friday. 36 hrs.

September 28-29—**Advanced Trauma Life Support Provider Course.** Emergency Shock Trauma Institute, Mercy Hospital at San Diego. Friday-Saturday. 16 hrs. $475. Contact: Emergency Shock Trauma Institute, Mercy Hospital, 4077 5th Ave., San Diego 92103. (619) 294-8111.

Octorber 13—**Emergency Medicine Oral Boards Part II.** Highland General Hospital at Hyatt Regency Hotel, Oakland. Saturday. $495. Contact: Robert H. Dailey. (415) 534-8055, Ext. 207.

October 29-30—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emer-

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OTHER USC OB/GYN OFFERINGS

PERINATAL MEDICINE
February 16-23, 1985
Royal Lahaina Hotel, Maui, Hawaii

Contact: Associate Dean, USC School of Medicine, Postgraduate Division, 2025 Zonal Avenue, KAM 307, Los Angeles, CA 90033. (213) 224-7051.

gency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

October 31-November 2—**EMS Today.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 19 hrs.

INTERNAL MEDICINE

July 20-22—**Infectious Disease.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 29-August 1—**Biomedical Ethics—Wilderness Horseback Conference.** Mercy Medical Center, Redding at Trinity Alps Wilderness. Sunday-Wednesday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 17-19—**2nd Annual La Jolla Summer Conference on Dermatology, Immunology and Rheumatology.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. Contact: Dianne Tisue, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

September 1-2—**Thyroid Today—1984: 3rd Annual Symposium.** See Of Interest to All Physicians, September 1-2.

September 10-15—**6th Comprehensive Nephrology Review Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Saturday. 38.5 hrs. $695.

September 15—**Neurology.** UCSF at Fresno. Saturday.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 19—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. Contact: Charles R. Beeson, MD, Assoc. Chief of Staff for Ed., VA Medical Center, 16111 Plummer St., Sepulveda 91343. (818) 891-2374.

September 19—**Controversial Problems of the Pancreas.** Cedars-Sinai Medical Center at Los Angeles. Wednesday. Contact: Lore Kahane, Cedars-Sinai Medical Center, PO Box 48750, Room 2049, Los Angeles 90048. (213) 855-5547.

September 21-22—**29th Annual Internal Medicine Symposium.** Kaiser Permanente Southern California Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. $150. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** See Allergy and Immunology, October 15-18.

October 17—**Diabetes—1984.** The Hospital of the Good Samaritan at Hyatt Regency Hotel Los Angeles, Los Angeles. Wednesday. Contact: Dolores Gay, Coordinator of Symposia, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

OBSTETRICS AND GYNECOLOGY

August 9-11—**Basic and Advanced Colposcopy.** American College of Obstetrics and Gynecology at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 12—**OB/GYN—Menstrual Disorders.** LLU. Wednesday.

September 28-29—**Outpatient Gynecology in the 1980's Progress and Expectations.** Center for Health Education at Long Beach. Friday-Saturday. 10 hrs. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 6—**Clinical Ultrasound—OB/GYN Update.** Sacramento Radiology Research and Education Foundation and the Northern California Radiology Society. Saturday. $75. Contact: J. P. McGahan, MD, Program Director, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 7-9—**The Neural and Metabolic Bases of Feeding.** See Pediatrics, October 7-9.

October 22-27—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** UCI. Monday-Saturday.

OPHTHALMOLOGY

July 26-27—**Ophthalmology Symposium.** UCI. Thursday-Friday.

August 25—**Neodymium: YAG Laser Workshop.** JSEI. Saturday.

October 10—**Ophthalmology-Therapeutic Decision re: Glaucoma, Retinopathy and Cataracts.** LLU. Wednesday.

October 11-13—**Cosmetic Blepharoplasty Workshop.** JSEI. Thursday-Saturday.

October 20—**Update for Nonophthalmologists: Ocular Diseases of Aging.** JSEI. Saturday.

PEDIATRICS

October 3-4—**41st Annual Brenneman Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Red Lion Motor Inn, Sacramento. Sunday-Tuesday.

October 20-27—**9th Annual Pediatrics for the Practitioner.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 26-27—**Adolescents Inside and Out.** Children's Hospital Medical Center of Northern California and California Chapter 1 of the American Academy of Pediatrics at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes-Dodd, Medical Staff Office, Children's Hospital Medical Center, 51st and Grove St., Oakland 94609. (415) 428-3334.

PSYCHIATRY

July 20-21—**Human Sexuality for the Health Professional.** Mental Research Institute, Palo Alto. Friday-Saturday. 10 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 23-27—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 28—**Treating Depression in a Marital Context.** Mental Research Institute. Palo Alto. Saturday. 5 hrs. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

July 29-August 2—**Mental Research Institute Summer Seminar** at Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-8—**Basic Hypnotherapy: Principles and Applications.** Mental Research Institute, Palo Alto. Monday-Wednesday. 6 hrs. $65. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 6-10—**Brief Therapy.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $175. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 8—**Continuing Medical Education Seminars—Psychiatry.** LLU. Wednesday.

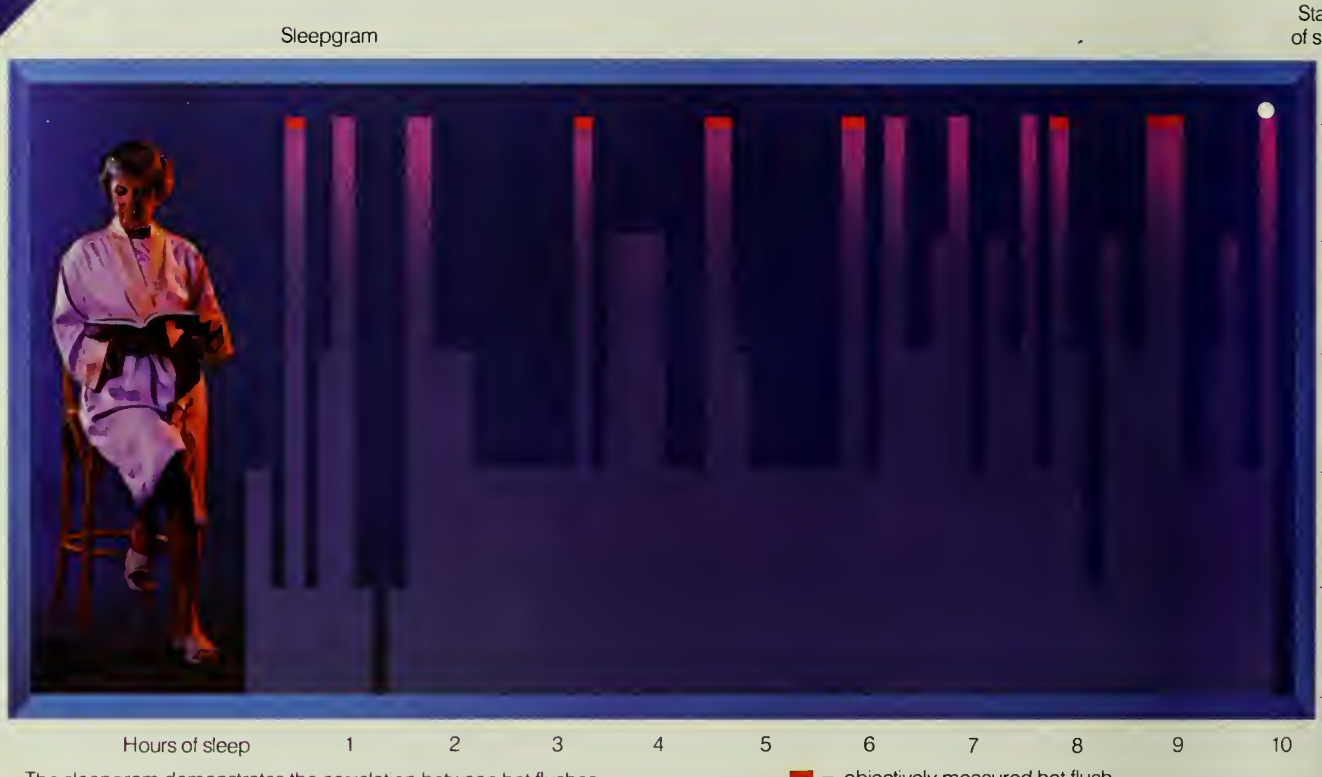
August 13-16—**Family Crisis: Intervention Strategies.** Mental Research Institute, Palo Alto. Monday-Thursday. 12 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 18-23—**Responsibility Issues in Mental Health.** Southern California Psychiatric Institute at Mauna Kea Beach Hotel, Kauela, HI. Saturday-Thursday. 15 hrs. Contact: Gail

(Continued on Page 40)

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

= objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

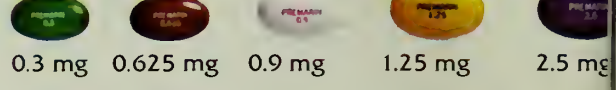
Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

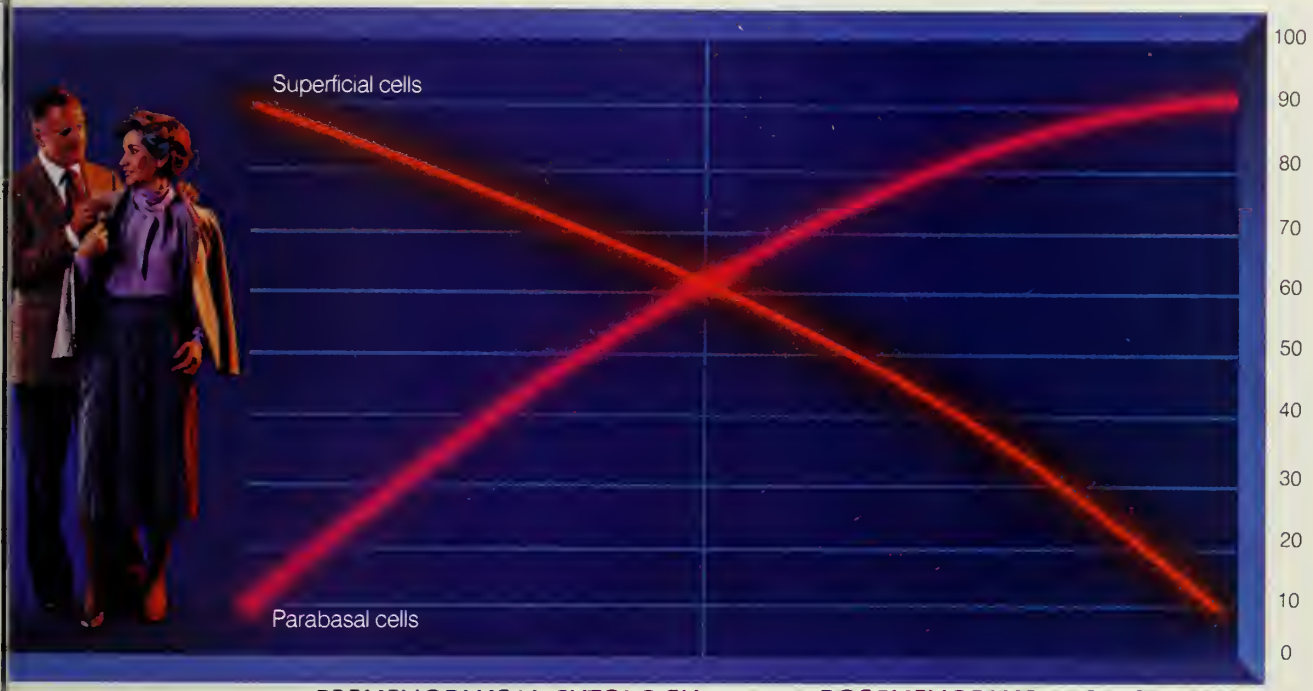
PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories

THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

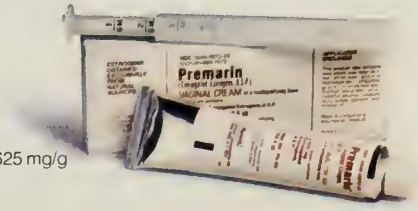
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

FOR ATROPHIC VAGINITIS

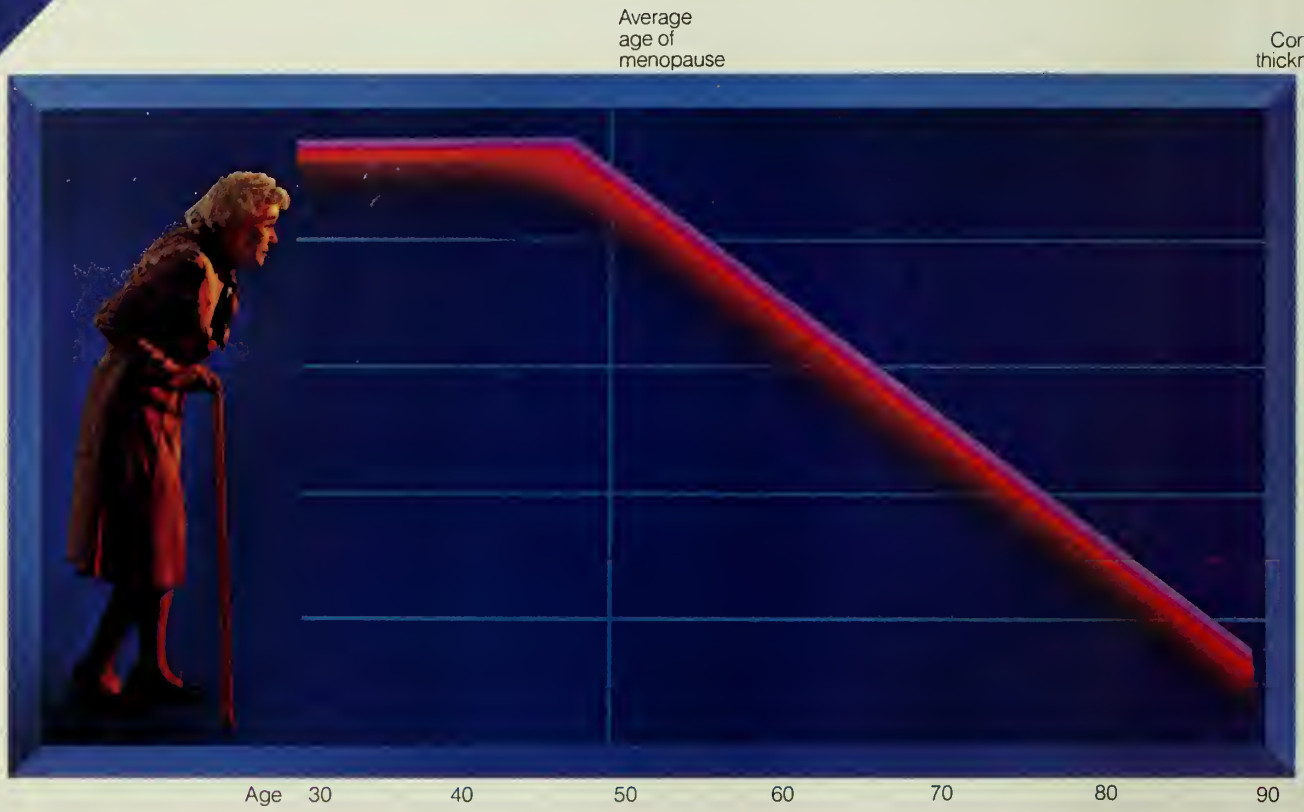
PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/g

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications for use as follows.

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma – palliative therapy of advanced disease
9. Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. Whether doses of this size are used in any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness; mental depression; chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism – 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure – 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression) – 1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement – 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer – 1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women – 10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865 – Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 – Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864 – Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867 – Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868 – Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream – No. 872 – Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available – Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube.

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(Continued from Page 35)

Waldron, MD, Program Dir., SCPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

August 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 25—**Case Studies in Brief Interactional Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

RADIOLOGY

August 20-24—**Radiology of the Abdomen.** UCSD at San Diego and Anaheim. Monday-Friday. 27 hrs. $395.

August 27-29—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and Northern California Radiological Society at Napa Valley. Monday-Wednesday. 18 hrs. $325. Contact: Michael H. Reid, MD, Program Dir., SRREF, PO Box 19184, Sacramento 95819.

September 6-9—**Physics of Diagnostic Radiology.** UCD. Thursday-Sunday. Contact: UCD (916) 752-0328.

September 8-9—**Head and Neck Radiology: Advanced Techniques in Diagnostic Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Saturday-Sunday. 12 hrs. $250. Contact: UCSF (415) 666-5731.

September 10—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Monday. 30.5 hrs. $400. Contact: UCSF (415) 666-5731.

September 15—**Radiotherapy and Surgery Symposium "Where Do We Stand With the Management of Localized Breast Cancer?"** Kaiser Permanente at The Biltmore Hotel, Los Angeles. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 17-20—**American College of Radiology Meeting** at Century Plaza Hotel, Los Angeles. Monday-Thursday. Contact: ACR, 20 N. Wacker Dr., Chicago 60606. (312) 236-4963.

October 13—**11th Annual Radiology Symposium.** Kaiser Permanente Southern California Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 13-21—**9th Annual International Body Imaging Conference.** West Park Hospital at Royal Lahaina Hotel, Maui. One week. 28 hrs. $425. Contact: Conference Sec., 9th Annual Body Imaging Conf., Dept. of Radiology, West Park Hospital, 22141 Roscoe Blvd., Canoga Park 91304. (818) 340-0580, ext. 280.

October 22-26—**9th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Monday-Friday.

SPORTS MEDICINE

July 20-22—**Sports Medicine and Cardiovascular Fitness—Whitewater Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

July 23-26—**10th Annual Meeting of American Orthopaedic Society for Sports Medicine** at Marriott Hotel, Anaheim. Monday-Thursday. Contact: AOSSM, PO Box 94274, Chicago 60690.

SURGERY

August 13-17—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

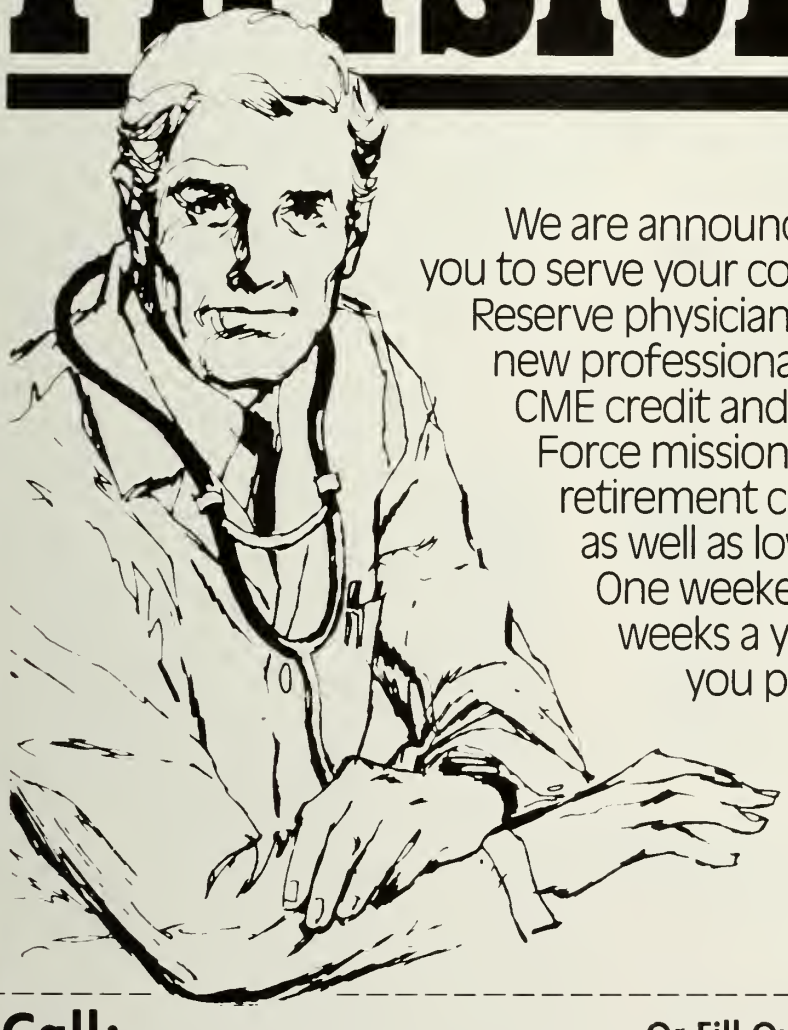
August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 17-21—**Basic Microsurgery Training**

(Continued on Page 42)

PHYSICIANS



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Phone _____ Prior Service? Yes ___ No ___

Medical Specialty _____ Date of Birth _____

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A GREAT WAY TO SERVE

(Continued from Page 40)

Workshop. UCSD. Monday-Friday. 34 hrs. $1,200.

September 20-22—**Microsurgery: An Introduction to Microtechnique for Small Artery and Nerve Repair.** American Academy of Orthopaedic Surgeons at San Diego. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

October 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

October 9-14—**American Society of Plastic and Reconstructive Surgeons Inc., American Society of Maxillofacial Surgeons Inc. and Plastic Surgery Educational Foundation Meeting** at Las Vegas. Tuesday-Sunday. Contact: ASPRS-PSEF, Exec. Office, 233 N. Michigan Ave., Ste. 1900, Chicago 60601.

October 10-14—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. 34 hrs. $1,200.

October 11-13—**Controversies in Urology.** American Urological Association at San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, PO Box 25147, Houston, TX 77265. (713) 799-6070.

October 14-18—**Western Orthopedic Association Meeting** at San Diego. Sunday-Thursday. Contact: WOA, 1970 Broadway, Ste. 1235, Oakland 94612. (415) 893-1257.

October 17-21—**Advanced Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. $1,200.

October 21-26—**American College of Surgeons Meeting** at San Francisco. Sunday-Friday. Contact: ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 24—**Spinal Update 1984.** UCSF at Hyatt Regency Hotel, San Francisco. Wednesday. 18 hrs. $295. Contact: UCSF (415) 666-5731.

October 26-29—**Total Knee and Hip Arthroplasty "Hands On" Course.** Center for Health Education, Long Beach. Friday-Monday. 20 hrs. Contact: Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

(Continued on Page 46)

RU-TUSS® II
sustained release capsules

Before prescribing, see complete prescribing information. The following is a brief summary.
DESCRIPTION: Each sustained release capsule contains 12 mg of chlorpheniramine maleate, USP and 75 mg of phenylpropanolamine hydrochloride, USP in a base to provide prolonged activity.
INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).
CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.
WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.
Usage in pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.
PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.
ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with chlorpheniramine maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, hypertension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis, leukopenia.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis hysteria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.
DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.
OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.
HOW SUPPLIED: Green and clear capsules with green and white beads. Bottles of 100 tablets. NDC 0524-0031-01
Store at controlled room temperature 15-30°C (59°-86°F.).
CAUTION: Federal law prohibits dispensing without prescription.

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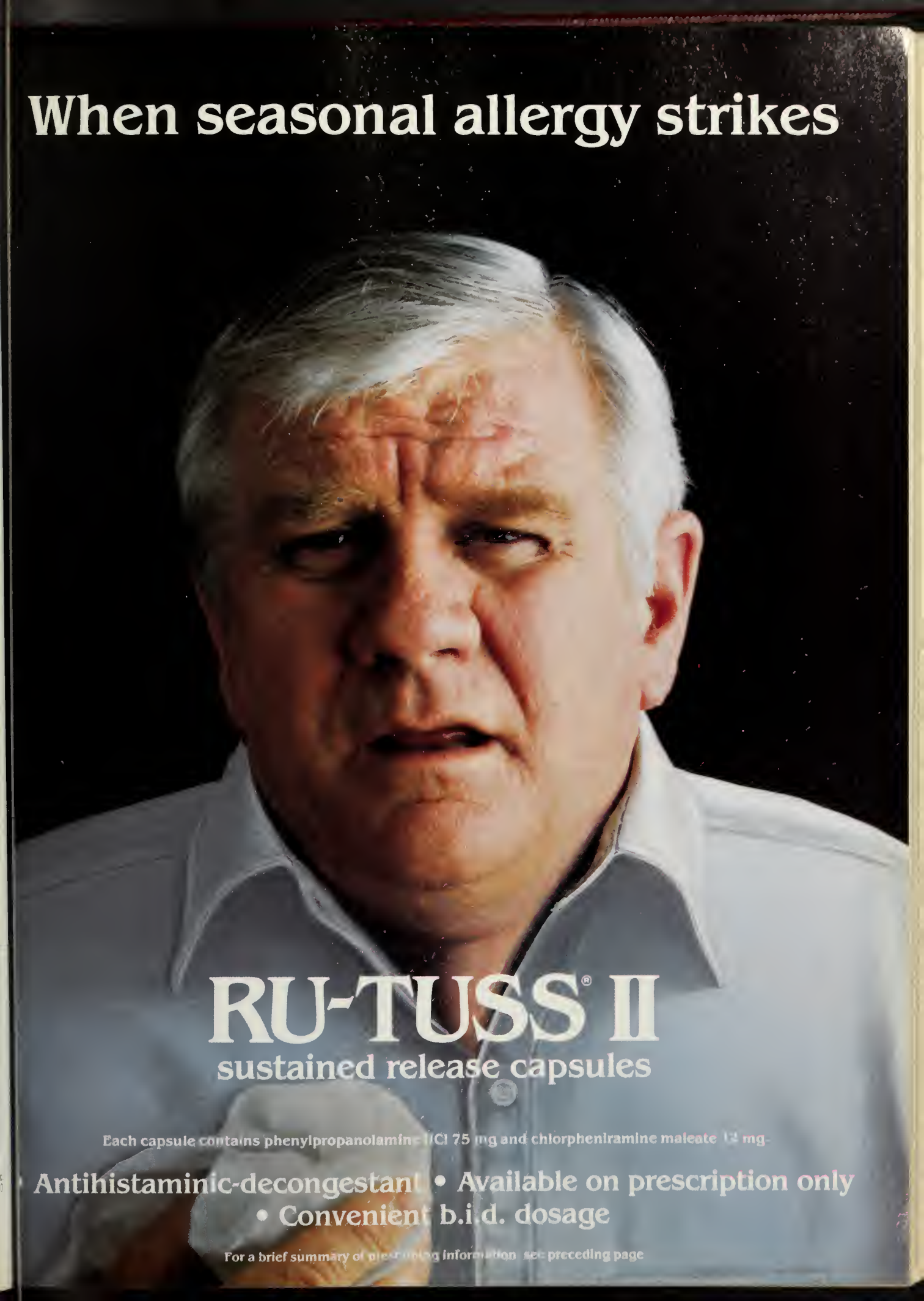

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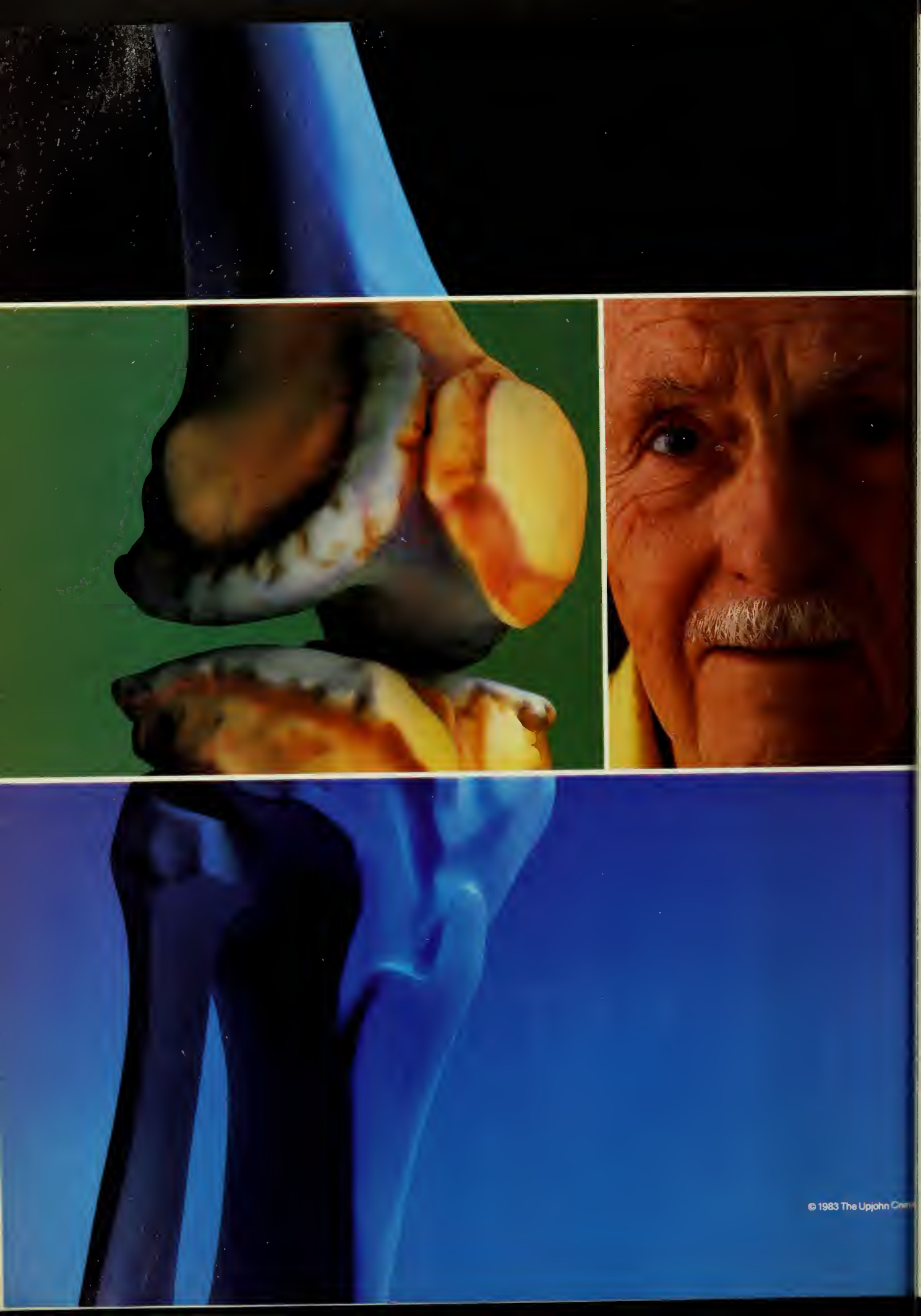
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Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

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The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS (ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported Ulceration, perforation and bleeding may end fatally An association has not been established Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing

Fluid retention and edema have been associated with *Motrin* Tablets, use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued

Drug interactions. *Aspirin*: used concomitantly may decrease *Motrin* blood levels

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence), **Central Nervous System:** Dizziness,* headache, nervousness, **Dermatologic:** Rash* (including maculopapular type), pruritus, **Special Senses:** Tinnitus, **Metabolic/Endocrine:** Decreased appetite, **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS)

Incidence less than 1%—Probable Causal Relationship

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests **Central Nervous System:** Depression, insomnia, confusion, emotional lability somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS), **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular**: Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations, **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria, **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis, **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis, **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia), **Metabolic/Endocrine**: Gynecomastia hypoglycemic reaction, **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia), **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin* (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day Mild to moderate pain 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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MED B-7-S

Upjohn

CONTINUING MEDICAL EDUCATION

(Continued from Page 42)

October 27—**Lumbar Spine and Pelvis.** UCSD at Hotel del Coronado, Coronado. Saturday.

October 28-November 9—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 29-November 3—**Basic Microsurgery Training Workshop.** UCSD at Surgery Research Lab, University Hospital, San Diego. Monday-Friday. $1,200.

OF INTEREST TO ALL PHYSICIANS

August 1-4—**Dermatology.** UCD at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday.

August 9-11—**Clinical Management of the Elderly Patient.** American Geriatrics Society at Fairmont Hotel, San Francisco. Thursday-Saturday. 15 hrs. $245. Contact: The American Geriatrics Society, 7201 Rossville Blvd., Baltimore, MD 21237, (301) 686-3610.

August 17-19—**Nutrition, Obesity, and Weight Control—White Water Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

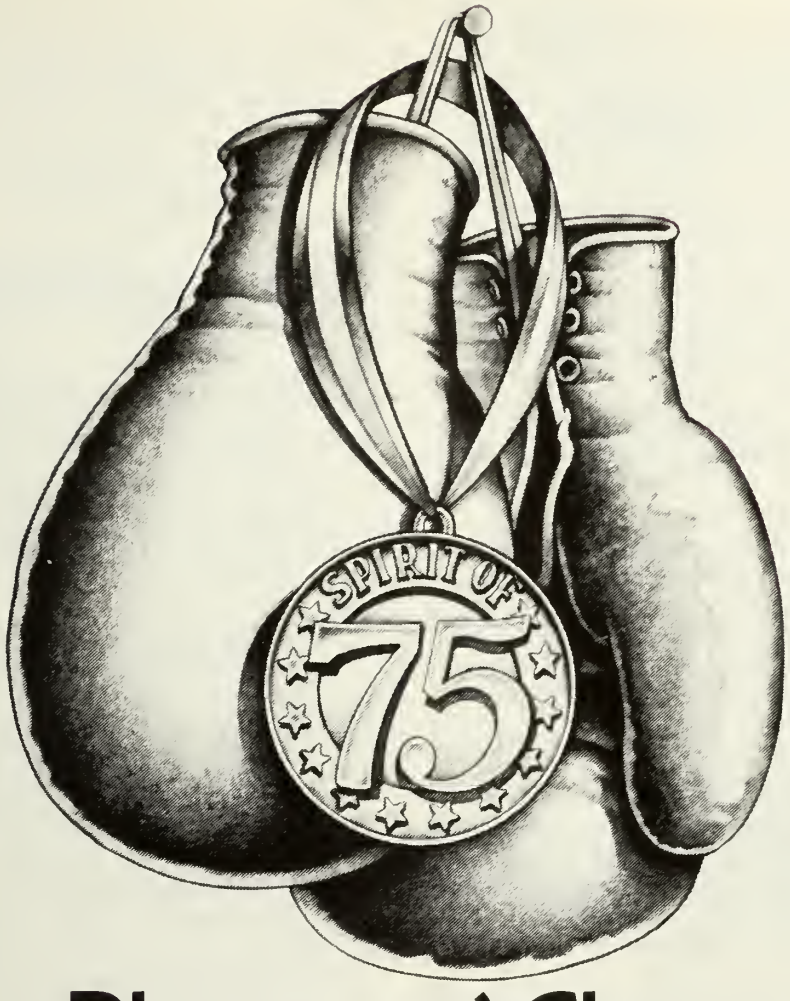
August 20-24—**CRYO '84: Course of Freezing of Animal Cells, Tissues and Organs.** UCD. Monday-Friday.

September 1—**Medical Mycology.** UCSF. Saturday.

September 1-2—**Thyroid Today—1984: 3rd Annual Symposium.** Cypress Foundation and Monterey County Medical Society at Doubletree Inn at Fisherman's Wharf, Monterey. Saturday-Sunday. Contact: Cypress Foundation, PO Box 80308, Salinas 93912. (408) 455-1833.

September 8-9—**Dermatopathology Board Review.** UCSF. Saturday-Sunday.

(Continued on Page 48)



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The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County, Ventura County.

(Continued from Page 46)

September 13-14—**Intensive Course in Adolescent Obesity.** UCSF. Thursday-Friday. $135.

September 17-19—**Relational Issues of Addiction: Violence, Sexuality and Intimacy.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, Conf. Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

September 17-21—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

September 19-21—**State of the Art in the Care of Geriatric Patients: Pre-Intra-Post-Operative Management.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $325. Contact: Robin B. Jackson, Office of Cont. Ed., PO Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

September 19-23—**Annual Scientific Program and Postgraduate Course of the Pacific Coast Fertility Society** at Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

September 20-23—**34th Annual Obesity and Associated Conditions Symposium.** American Society of Bariatric Physicians at MGM Grand Hotel, Reno. Thursday-Sunday. 17 hrs. Contact: Randall B. Lee, Exec. Dir., 4730 E. Caley Ave., Ste. 210, Englewood, CO 80111. (303) 779-4833.

September 21—**Dermatology and Dermatologic Office Procedure Workshop.** CME at Kona Kai Club, San Diego. Friday. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 23—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. $175. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 29—**Food Allergy: Update 1984.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Geri Coldewey, LASACI, 1626 North Wilcox, #557, Hollywood 90028.

October 1—**Nutrition Symposium.** UCSF at Yosemite. Monday.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Tuesday.

October 8-19—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

October 11-14—**A California Conference in Applied Clinical Geriatrics.** UCD at Napa Valley. Thursday-Sunday.

October 12-13—**Skin From A to Z.** UCSF. Friday-Saturday.

October 12-13—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $200.

October 12-14—**28th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Holiday Inn Golden Gateway, San Francisco. Friday-Sunday. 10 hrs. Contact: Joe Donovan, c/o WOMA, 433 Palmer Ave., Aptos 95001. (408) 688-0667.

October 16-18—**Primary Medical Care of Selected Infectious Diseases.** Health Science Seminars of UCSF at Sheraton Hotel, Poipu Beach, Kauai, HI. Tuesday-Thursday. $225. Contact: Cynthia Vaughan, Program Coordinator, PO Box 22023, San Francisco 94122. (415) 861-2713.

October 17—**Second Annual Alcohol & Drug Dependencies Symposium.** Kaiser Permanente Southern California at The Pasadena Hilton, Pasadena. Wednesday. $90. Contact: Judy Harrison—Dept. of Clinical Services, Kaiser-Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 19-21—**Medical Mycology.** UCSF. Friday-Saturday.

October 25-27—**Postgraduate Institute.** CMA at Monterey Sheraton, Monterey. Thursday-Saturday. $150—Non-member, $100—Member. Contact: Janice Rigney (415) 863-5522 Ext. 416.

October 29-November 1—**Interstate Postgraduate**

Medical Association Meeting at Las Vegas. Monday-Thursday. Contact: H. B. Maroney, Exec. Dir., PO Box 1109, Madison, WI 53701. (608) 257-6781.

IDAHO

July 25-28—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, 407 W. Bannock St., PO Box 2668, Boise 83701.

August 5-11; 12-18—**Computers in Professional Practice: An EPIC Medical Expedition.** Tyrolean Lodge, Sun Valley. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 15-21—**Updates in Pediatrics: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 18-19—**Trauma Update—84.** North Shore Convention Center, Lake Coeur d'Alene. Contact: Linda Ady, Conf. Coordinator, Idaho EMS System, 450 W. State St., Boise 83720. (208) 334-4245.

September 9-14—**Up-to-Date Cardiac Therapy: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. Sunday-Friday. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 18-24—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** Fishing and Chukar hunting adventure on the Main Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of

(Continued on Page 51)

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(Continued from Page 49)

Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

September 21-22—**American College of Physicians—Regional Meeting.** Heritage Inn, Great Falls. Friday-Saturday. Contact: Warren D. Bowman, Jr, MD, Billings Clinic, Box 2555, Billings 59103.

October 4-6—**Montana Medical Association Annual Meeting.** Sheraton, Billings. Thursday-Saturday. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (500) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 16-19—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I, NM Cat. IV, AAFP Prescribed. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

(Continued on Page 136)

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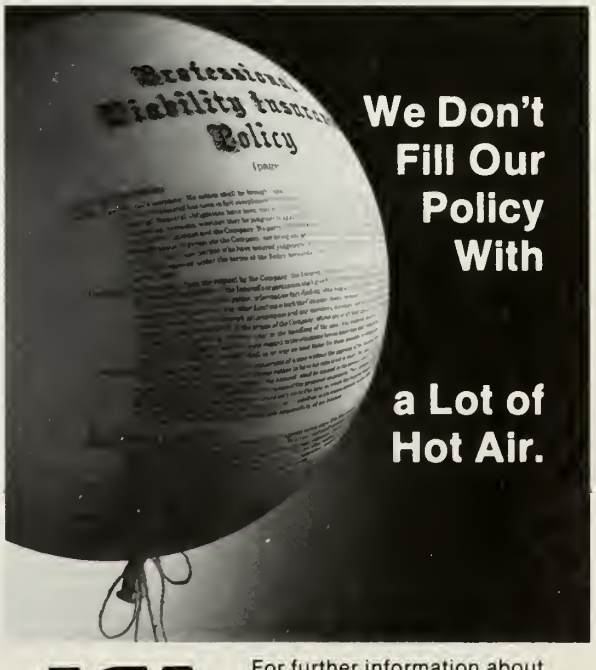

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Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide, dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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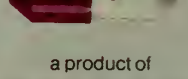

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Campylobacter Enteritis on Hopi and Navajo Indian Reservations

Clinical and Epidemiologic Features

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From June 22 through September 30, 1981, stool specimens from 522 Hopi and Navajo outpatients were cultured because of diarrheal illnesses at the Keams Canyon Indian Health Service Hospital, Arizona. Campylobacter jejuni *was isolated from the specimens of 26 (5%) of the patients. This pathogen was found as frequently as* Shigella *in patients younger than 2 years or older than 20 years, but was significantly less common in the 2- to 20-year age group (*P<*.000001).* Campylobacter *enteritis was indistinguishable clinically from shigellosis in adult patients, but in children younger than 5 years, a rectal temperature higher than 38°C (100.5°F) was significantly more common with* Shigella *than with* Campylobacter *infection (*P=*.003). In a field study of 20 families, we found that households with a case of* Campylobacter *enteritis were more likely than age- and community-matched controls to own farm animals (*P=*.05), but were not more likely to own household pets.* C jejuni *is less common than* Shigella *as a cause of summer seasonal diarrhea and dysentery among the Hopi and Navajos; the striking differences in the age-specific rates of these two infections suggest different routes of transmission.*

(Engleberg NC, Correa-Villaseñor A, North CQ, et al: *Campylobacter* enteritis on Hopi and Navajo Indian reservations—Clinical and epidemiologic features. West J Med 1984 Jul; 141:53-56)

Indian Health Service physicians report 45 to 66 new visits for "bacillary dysentery" per 10,000 Indian population per year, with the highest rates reported from southwestern tribes.[1] Before the recognition of *Campylobacter jejuni* as a common invasive enteric pathogen, it was assumed that these dysenteric illnesses were due principally to *Shigella* infection.[2] Because the symptoms of bloody diarrhea or fever are reported by most patients with *Campylobacter* enteritis, the clinical illness associated with this pathogen is often indistinguishable from shigellosis.[3-5] Because Indian Health Service case reports are based on clinical impression, we suspected that part of the excessive "dysentery" morbidity could be attributed to *Campylobacter* enteritis.

During the past decade, *C jejuni* has been associated with 3% to 14% of cases of clinical diarrhea in studies from developed countries.[3-8] In these clinic-based studies, *C jejuni* was most commonly associated with diarrhea in young adults and was relatively less common in infants and young children. Identification of the organism in stool specimens of healthy persons was rare.[6-8] In contrast, studies from developing countries suggest a much higher prevalence and a different age distribution of *C jejuni* infection. In Bangladesh, *C jejuni* was most commonly found in stool specimens

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from infants and young children who had diarrhea and was also found in specimens from 17.7% of healthy children.[9] These conflicting studies suggest that the epidemiology of *Campylobacter* enteritis differs in developed and developing countries. Because the epidemiology has not been described in an American Indian population, we designed this study to measure the proportion of cases of clinical dysentery associated with *C jejuni* among Indian patients, to define the age groups that are predominantly affected and to determine whether *C jejuni* and *Shigella* infections could be distinguished by clinical criteria or patient characteristics.

The study was conducted at the Keams Canyon Indian Hospital in northeastern Arizona, an Indian Health Service facility that serves about equal populations of Hopi and Navajos. Traditionally, the Hopi are village-dwelling agriculturalists,[10] whereas the Navajo live in scattered family encampments and are principally engaged in raising sheep or cattle in close proximity to their dwellings.[11] These farm animals are potential hosts for *C jejuni*.[12] Human *Campylobacter* infections have been associated with infection of household pets[13] and with drinking unpasteurized milk from dairies with infected cows.[14] Using cases identified by fecal culture at the hospital outpatient clinics, we conducted a controlled field investigation to determine how environmental and life-style factors—particularly contact between humans and animals—may have influenced the occurrence of *C jejuni* infection on these two reservations.

Patients and Methods

Cultures for *C jejuni*[6] and *Shigella,* using standard methods, were done in all patients with diarrhea seen at the Keams Canyon Hospital or field clinics between June 22 and September 31, 1981. All *Campylobacter* isolates were biochemically confirmed by the Enteric Bacteriology Section, Enteric Diseases Branch, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta.[12] Cases of diarrhea that were reported to the Indian Health Service surveillance system by hospital staff physicians as cases of "bacillary dysentery" were reviewed to determine, retrospectively, what proportion were associated with *C jejuni* or *Shigella.*

The age, sex and tribe of all patients in whom stool cultures were done during the study period were determined by medical records personnel, using the patient's identification number from laboratory logbooks. The medical records of all patients with *Campylobacter*-positive cultures were reviewed to record the staff physician's clinical observations at the time the specimen was obtained—that is, patient's body temperature, appearance of the stool and results of stool microscopic examination. The findings from these records were compared with those of 37 patients with *Shigella*-positive cultures (29 *Shigella flexneri,* 8 *Shigella sonnei*) during the same period who were selected if they had negative cultures for *Campylobacter,* they lived within the service area of Keams Canyon Hospital and their medical records were available for review at the hospital.

In the period June 22 to September 11, 1981, we visited the homes of *Campylobacter*-positive patients who were residents of the Hopi Reservation or the surrounding Navajo Reservation communities of Low Mountain, Jeddito, Whitecone and Pinon within ten days of the initial clinic visit. At each household, we interviewed all available family members using a pretested questionnaire to record any recent diarrheal illnesses in household contacts and to collect information about the home environment, including the ownership of and contact with domestic animals, the presence or absence of indoor plumbing and patterns of household water use. We determined total household water use in homes lacking tap water by noting the volume of water storage containers and the stated frequency of refilling. Rectal swab specimens were collected from adult household members who gave informed consent and from assenting minors whose parents gave consent. Rectal swab specimens were also collected from household animals with consent of the owners.

To evaluate potential household risk factors, we selected controls from among Keams Canyon Clinic patients without diarrhea seen during the same time period as persons ill with *C jejuni* and *Shigella* infections. Controls were matched by age group (4 years and younger, 5 to 14 years, 15 to 44 years and 45 years and older) and by community of residence. Matching by community also matched for tribe. Control-families were visited and interviewed by the same methods used for case-families.

Results

C jejuni was identified in the stool specimens of 26 (5.0%) of the 522 patients who had diarrhea during the surveillance period, 6 (6.7%) of the 89 patients reported to have had bacillary dysentery and 20 (4.6%) of the 433 patients who had diarrhea but not bacillary dysentery. *Shigella* was identified in specimens of 13.4% of all patients with diarrhea, 25.8% of the patients with bacillary dysentery and 10.9% of patients with diarrhea but not bacillary dysentery. Patients reported to have bacillary dysentery were significantly more likely than all other diarrhea patients to have *Shigella* identified in their feces ($\chi^2 = 13.0$; $P < .001$). The clinical impression of bacillary dysentery was not associated with isolation of *Campylobacter* ($\chi^2 = 0.3$).

Campylobacter was found most frequently in the stool specimens of children younger than 2 years and of adults older than 20 years (Table 1). In children younger than 2 years, the rates of *Campylobacter* and *Shigella* isolation were not significantly different; however, *Shigella* was identified ten times more often than *Campylobacter* in patients 2 to 14 years of age, a significant difference when compared with younger children ($P = .002$; χ^2). *Campylobacter* was more common in Navajo (6.3%) than in Hopi patients (3.4%), particularly among patients aged 10 years or older; how-

ever, these tribal differences were not statistically significant (Table 2).

Medical records were obtained for 21 of the 23 patients who had diarrhea and in whom *Campylobacter* was the only bacterial pathogen identified in their stool specimens. When these 21 cases were compared with 37 *Shigella*-positive cases, there were no statistically significant differences in the clinical presentations. Staff physicians empirically treated patients in both groups with antimicrobials with similar frequency (62% and 80%, respectively). When children and adult patients were considered separately, differences in the clinical presentations became apparent. Only 6 (40%) of the 15 *Campylobacter*-positive children younger than 5 years were febrile at presentation (temperature 38.1°C [100.5°F] or higher) compared with 13 (100%) of 13 *Shigella*-positive children in the same age group ($P = .003$; Fisher's exact test, two-tailed). *Campylobacter*-positive children also had a lower median rectal temperature (38°C [100.4°F]; range 35.9°C to 39.9°C) than did *Shigella*-positive children (39.7°C [103.4°F]; range, 38.1°C to 40.2°C; $P = .0005$; Mann-Whitney U test). The median oral temperatures for patients aged 5 years and older were similar in the two pathogen-specific groups (37.7°C [99.9°F]). In children younger than 5 years, there was also some evidence (though not statistically significant) to suggest that *Campylobacter*-positive patients were less likely than *Shigella*-positive patients to have gross blood in the stool ($P = .06$) or more than ten polymorphonuclear leukocytes per high-power field on fecal examination ($P = .06$). The clinical illness associated with *S flexneri* and *S sonnei* infections were similar by all measured criteria.

TABLE 1.—Campylobacter jejuni *and* Shigella *spp Isolations From 522 Outpatients Who Had Diarrhea, by Patients' Age, Keams Canyon Indian Health Service Hospital, June 22 to September 30, 1981*

Age Group	Stool Specimens Cultured Number	Positive for C jejuni Number (Percent)	Positive for Shigella Number (Percent)
0-11 mo	153	8* (5.2)	7* (4.6)
12-23 mo	56	5 (8.9)	9 (16.1)
2- 4 yr	51	2 (3.9)	17 (33.3)
5- 9 yr	27	1 (3.7)	7 (25.9)
10-14 yr	23	0 (. . .)	10 (43.5)
15-19 yr	15	0 (. . .)	1 (6.7)
20-39 yr	71	3* (4.2)	4* (5.6)
40-59 yr	58	3 (5.2)	9 (15.5)
60+ yr	54	2* (3.7)	6* (11.1)
Unknown	14	2 (14.3)	0 (. . .)
TOTAL	522	26 (5.0)	70 (13.4)

*One patient in each group had both *C jejuni* and *Shigella flexneri*.

TABLE 2.—Campylobacter jejuni *Identified in Hopi and Navajo Patients With Diarrhea, by Tribe and Age Group*

Age Group	Positive Isolates/Tested: Hopi Number (Percent)	Navajo Number (Percent)
<10 yrs	6/118 (5.1)	8/135 (5.9)
>10 yrs	2/66 (3.0)	6/77 (7.8)
All*	8/233 (3.4)	17/268 (6.3)

*Includes patients of unknown age.

TABLE 3.—*Animal Ownership by Ten Households of* Campylobacter *Enteritis Patients and Matched Control Households*

Animals	Case-Households Number	Control-Households Number
Pets	8	8
Dogs	7	8
Cats	6	6
Farm animals	7*	1*
Poultry	2	1
Sheep	3	1
Goats	2	1
Cows	0	1
Horses	2	1
Rabbits	2	0
All animals	9	9

*$P = .05$, McNemar's test.

In the household studies, diarrheal illnesses occurred in 4 (8%) of the 53 household contacts of cases and in 1 (2%) of the 49 household contacts of controls ($P = .4$; χ^2). Cultures were done in 6 of the 28 children younger than 15 years but none were positive for *C jejuni*. We also did cultures in nine cats, six dogs, eight sheep and five trapped rodents. The cultures of one cat and two dogs were positive for *C jejuni*.

In the ten case-households and ten matched controls, we found no association between cases and ownership of any single animal species; however, case-households were significantly more likely than controls to own farm animals (poultry, cattle, sheep, goats, horses or rabbits) ($P = .05$; McNemar's test). Ownership of household animals (dogs or cats) was similar in case- and control-households (Table 3).

Only 2 of the 20 households had indoor tap water (both were control households). The remaining 18 households obtained water from closed wells. If an estimate of 60 gal per household per day (based on community water system readings) is assumed for the two controls, then the median daily water use was less in case-households (8.0 gal) than in control-households (14.4 gal, $P = .04$, Wilcoxon test). Likewise, if homes with tap water are considered to have unlimited "storage" capacity, median household water storage capacity was less in case-households (47 gal) than in control-households (65 gal, $P = .04$).

Discussion

During the summer of 1981, *C jejuni* was identified in the stool specimens of 5.0% of Hopi and Navajo outpatients who had diarrhea, a frequency of isolation similar to that reported in other US populations.[3-5] During the same period, *Shigella* was found in 13.4% of our patients. Because geography and economics make routine follow-up difficult, antimicrobials are often used empirically by Indian Health Service physicians. An analysis of cases of diarrhea by the physician's clinical impression suggests that the reported

diagnosis of bacillary dysentery was associated with subsequent identification of *Shigella,* but was not predictive of *Campylobacter* infection. We therefore compared culture-proved cases of *Campylobacter* and *Shigella* enteritis to determine whether these infections could be distinguished on clinical grounds. Although we found no distinctive clinical features of *Campylobacter* infections, the diagnosis of shigellosis was strongly favored if the patient was between 2 and 14 years of age or had fever on presentation. For adults older than 20 years, the frequency of isolation of the two pathogens did not differ significantly, and there were no distinguishing clinical features.

In the ten households of *Campylobacter*-positive patients, diarrheal illness occurred in only 8% of household contacts; without knowing the source of infection for the index cases, however, the interpretation of this finding is difficult. In a recent study in Colorado, Blaser and associates interviewed and cultured specimens from household contacts within 48 hours of the identification of a *Campylobacter* case; 15% reported a diarrheal illness, and the stool specimens of 8 of the 12 ill contacts were positive for *C jejuni.*[15] In the only ill contact from whom we obtained a specimen, culture was negative for *C jejuni,* and the diarrhea attack rate in our case-households was not significantly different from that in control-households. Because we allowed up to ten days to locate the case-families, recall bias may have occurred in some instances, causing an underestimate of the household attack rates.

The association between cases and the ownership of farm animals probably explains why infection was more common in Navajo than in Hopi patients. Animals may be a source of infection for humans through direct contact or by ingesting unpasteurized milk or improperly cooked foods.[3,14] In this study, *Campylobacter* illness was not associated with household dogs, puppies, cats or kittens. Unpasteurized milk is not available at any of the reservation stores; families that own cows or goats do not milk them for home use. Although locally slaughtered mutton is frequently eaten, it is stewed thoroughly in most preparations. However, cross-contamination of cooking utensils or cutting surfaces by raw meat is a possible mechanism of transmission. Alternatively, transmission could occur during direct contact with farm animals, such as during the handling or shearing of sheep.

The association between low household water use or water storage capacity and *Campylobacter* enteritis may be related to inadequate amounts of water for personal hygiene. The unavailability of water is known to promote the person-to-person transmission of *Shigella,*[16,17] but this mode of transmission has rarely been suggested for *Campylobacter.*[18] Water has also been implicated as a vehicle of transmission in a few outbreaks[19,20]; it is an unlikely source of infection on the reservations because the cases were evenly distributed to several communities with independent water systems (all using ground water as a source). In general, families with adequate home water supplies live in new housing in village communities where farm animals are less likely to be kept, whereas families engaged in herding or ranching live in geographically isolated areas where water distribution systems do not exist. Because of the small number of households in the study, we could not determine which of these factors was most important.

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Perilymphatic Fistula—A Definitive and Curable Cause of Vertigo Following Head Trauma

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Vertigo or disequilibrium occurring in patients after concussive and nonconcussive head trauma may be due to a pathologic perilymphatic fistula from the inner ear through the oval and round window areas of the middle ear. Of 33 patients who had successful grafting of the fistulous area at middle ear exploration, 32 had resolution of vertigo, and 12 of 23 who had an associated hearing loss had improved hearing. Perilymphatic fistulas associated with vertigo and hearing loss after head trauma can be diagnosed with great certainty and are surgically curable in the great majority of cases. Patients with postconcussive syndrome, whose symptoms include vertigo or disequilibrium, should have a thorough otologic evaluation for the possibility of a perilymphatic fistula.

(Lehrer JF, Rubin RC, Poole DC, et al: Perilymphatic fistula—A definitive and curable cause of vertigo following head trauma. West J Med 1984 Jul; 141:57-60)

The postconcussional symptom complex resulting from minor or severe head injury includes vertigo.[1] The vertigo, which can initially occur in 35% to 40% of patients, is a persistent complaint in 26% of patients even ten years after the initial trauma.[2] Such patients may have disequilibrium, or vertigo that occurs only with a change of head position. Otologists have described the entity of posttraumatic perilymphatic fistula as an explanation for postconcussive vertigo but have not reported this in the general medical literature. In this report we review the techniques of diagnosis and surgical treatment of this condition and describe the newer diagnostic methods, the findings and the outcomes in 33 patients with surgically confirmed posttraumatic perilymphatic fistula.

Fee[3] reported finding fistulous leaks of perilymph in the area of the oval window while doing a middle ear exploration in two patients who had persistent vertigo after head trauma. Resolution of the vertigo occurred in both cases after tissue grafting of the affected area was done. Healy and co-workers[4] reported oval and round window perilymphatic fistulas in 21 patients who had suffered previous blunt head trauma. They stated that "severe or even mild head trauma is the most common precipitating factor of perilymphatic leaks. All patients with a history of trauma who complain of unsteadiness, vertigo or tinnitus are 'suspects.' "

The sensory organs of balance and hearing in the inner ear are suspended between endolymph, a potassium-rich fluid, and perilymph, a potassium-poor and sodium-rich fluid that is similar to cerebrospinal fluid. The stapes bone inserts into the oval window whereas the round window is covered by a membrane that separates the middle ear from the basal turn of the cochlea. Both of these windows, which can be visualized in the middle ear, abut on the perilymphatic space of the inner ear. Concussive and nonconcussive head injuries have been reported to cause vertigo and hearing loss with pathologic changes being found in the middle ear, cochlea and vestibular nuclei but "the

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Submitted October 13, 1983.

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TABLE 1.—*Classification of Head Trauma and Site of Perilymphatic Fistula in 33 Patients Surgically Treated for Vertigo*

Classification of Head Trauma	Total	Site of Fistula			Symptoms		Course of Vertigo After Surgical Treatment		
		Round	Oval	Both	Vertigo Only	Vertigo With Hearing Loss	Resolved	Persistent	Recurrent
		Number of Patients			Number of Patients		Number of Patients		
Concussive	12	3	6	3	4	8	10	..	2
Nonconcussive	12	3	5	4	4	8	9	..	3
Questionable	9	4	3	2	2	7	6	1	2
TOTALS	33	10	14	9	10	23	25	1	7

mechanism of injury to the vestibular system from a blow to the head cannot be defined as clearly as for the auditory system."[5(p297)] It would indeed be difficult, if not impossible, to demonstrate the minute fistulous pathway associated with posttraumatic perilymphatic fistula on pathologic examination of the temporal bone.

In our preliminary report[6] we described finding this type of fistula in three patients who had vertigo after head trauma. In our series of 65 cases of surgically confirmed perilymphatic fistulas, antecedent head trauma occurred in 33. Of these, 21 patients sustained head trauma in motor vehicle accidents, six in falls, two were victims of assaults and the other four suffered various other forms of head trauma. Table 1 shows the site of the fistula in these patients, 12 of whom suffered definite concussions. Although vertigo was the presenting symptom in every case, a hearing loss was detected in almost 70% of these patients. The typical loss was a mild fluctuating sensorineural one in the ear with the fistula. Positional vertigo, with accompanying positional nystagmus, was the presenting complaint in five patients. The most common type of vertigo noted was persistent disequilibrium, which was present in 28 patients. This symptom is quite different from the severe vertigo and ataxia experienced by patients suffering an acute unilateral loss of vestibular function whose symptoms, though more severe, usually resolve in four to six weeks due to central compensatory mechanisms.[7] Patients with posttraumatic perilymphatic fistula also differ substantially from those who have Meniere's disease. The pronounced subjective fluctuations in hearing and disabling attacks of vertigo lasting for several hours, while typical of Meniere's disease, did not occur in our patients, nor did they have the symptoms of ear pressure and distracting tinnitus noted by patients with Meniere's disease. Only mild ear fullness and tinnitus were described by our patients.

Diagnostic Methods

Fee[3] felt that a posttraumatic perilymphatic fistula should be suspected in cases of vertigo and hearing loss following head injury but offered no specific tests. Healy and associates described a syndrome of ataxia, vertigo that could be positional, tinnitus and hearing loss following head trauma. They were concerned that negative explorations of the middle ear would occur and hoped that further diagnostic measures would be developed. The fistula test has been a major advance in diagnosis. Inducing a pressure change in the middle ear by creating positive and negative pressures in the external auditory canal can cause vertigo in patients with perilymphatic fistulas. We have used the impedance bridge in doing this test, creating a positive pressure of 400 mm of water and then gradually changing the pressure to a negative pressure of 400 mm of water. Kohut and colleagues[8] have described positive findings in patients who had fistulas. Nadol[9] reported negative findings in normal patients but a positive sign in 30% of patients with a diagnosis of Meniere's disease in the affected ear. However, several of these patients had had otologic trauma and may well have had a posttraumatic perilymphatic fistula. Nevertheless, positive results of a fistula test in a patient with Meniere's disease without a history of head or otologic trauma should be interpreted with caution to prevent unnecessary middle ear explorations in these cases.

A complete evaluation of the hearing function is always done. It should be noted that although all of these reported patients had vertigo, ten had normal hearing. The vestibular evaluation must include a Romberg test and a Quix test for body sway and tests for spontaneous and positional nystagmus. Electronystagmography is routinely done though we have not found the results to be definitive. A reduction of function in the affected ear has been reported by Love and Waquespack.[10] When positional nystagmus is present on physical examination, it is usually directed towards the affected ear and is most severe when that ear is turned towards the ground. Results of the Romberg test are usually normal. We have found the Quix test[11] for body deviation extremely valuable. This test is done by having the patient stand with feet together, eyes closed, chin raised and arms and index fingers extended. A reproducible gradual sway in a lateral direction is viewed as a positive finding. The deviation occurred towards the affected ear in those cases with normal hearing but, in cases of hearing loss, was often in a direction away from the affected ear.

The glycerin test has provided valuable confirmatory evidence in cases of posttraumatic perilymphatic fistula.[12] The test is done by reevaluating the abnormalities found on the hearing and vestibular physical examinations at 30-minute intervals over a three-hour period after a patient has ingested 1.2 ml of glycerin per kg of body weight. A temporary reversal of the abnormal findings occurs after the ingestion of glycerin in much the same fashion as is found in patients with

TABLE 2.—*Improvement in Hearing in 17 Patients After Surgical Treatment of Posttraumatic Perilymphatic Fistula*

Decibel Improvement dB	*Number of Patients*
<10	5
10-20	5
20-30	6
>30	1

*Categories of Improvement**	*Mean dB Improvement†*	*Number of Patients*
1	10	5
2	21	8
3	14	4

*Categories:
1. Initial hearing normal but further improved postoperatively.
2. Below-normal hearing improved to normal hearing.
3. Hearing improved but not to normal levels.

†Average of 250 Hz, 500 Hz, 1 kHz and 2 kHz.

Meniere's disease.[13] Patients who have perilymphatic fistula have probably been misdiagnosed as having Meniere's disease. The differences in clinical presentation have already been outlined.

Surgical Technique

Surgical intervention in this group of patients was done between 1 and 48 months after the head injury, with a mean time between injury and the procedure of 10 months. A middle ear exploration is carried out under general or local anesthesia. The operation is done through an ear speculum inserted in the external auditory canal. The tympanic membrane is elevated in continuity with a canal wall skin flap and the middle ear entered. An operating microscope with high magnification and two-source illumination is used. The patient is placed in a Trendelenburg position, which increases the cerebral venous pressure and, consequently, the cerebrospinal and perilymphatic fluid pressures. The cochlear aqueduct is the best-defined channel through which the cerebrospinal fluid communicates with perilymph, though other smaller, inner ear pathways appear to exist.[14] The resultant increase in perilymphatic fluid pressure increases fistulous leaks into the middle ear and facilitates identification of the area of the fistula. Pressure on the internal jugular vein has also been used to accomplish this purpose. The areas of the round and oval windows and, especially, the area anterior to the oval window (fissula ante fenestram) are all carefully observed. Manipulation of these areas is not done until a diagnosis of a fistula is made. The surgeon looks for clear fluid appearing in any of these areas that recurs after gentle suctioning with a fine suction. The bony overhang in the round window niche may need to be removed to completely inspect the round window membrane and niche. Fine adhesions are often found in the middle ear in the area of the fistula. These may well be the middle ear correlate of the vestibulofibrosis described by Nadol in patients with positive fistula tests and vertigo.[15] If the fistula is found anterior to the oval window, the procedure is to denude the middle ear mucosa in that area and seal the area with a tissue graft. Earlobe fat, perichondrium and subcutaneous tissue have all been used for grafting purposes. Gelatin sponge (Gelfoam) is used to support the grafts once they are in place. If a stapedial fracture is found or if the stapedial footplate is the site of the leak, a stapedectomy with insertion of a prosthesis and tissue graft is indicated.

Fistulas in the round window area can be due to actual perforations in the round window membrane. The tissue graft is placed against these perforations and supported by Gelfoam. If a fistula is found in the round window niche adjacent to the round window membrane, the mucosa is denuded and a tissue graft supported by Gelfoam is applied. During the two to three days in hospital postoperatively, bed rest or rest in a chair is imperative. Patients are cautioned against straining, coughing, sneezing with the mouth closed or blowing of the nose, all of which can increase the pressure in the middle and inner ear. Ambulation should be resumed gradually and a modified rest program is instituted for a three-month period. The patient may return to work two weeks after the operation but should not be in a job situation demanding physical exertion. Female patients are cautioned concerning future pregnancies as recurrences have occurred in several of these patients due to the straining associated with delivery.

Results

All but one patient had complete resolution of the presenting complaint of vertigo with resolution of abnormal physical findings. Of 23 patients with hearing loss, 17 had an improvement in hearing. The mean improvement, as shown in Table 2, was between 10 and 21 dB. The five patients who required stapedectomy, three of whom suffered concussions, were in that group that did not show a hearing improvement. Only one patient continued to have subjective complaints of lightheadedness and occasional disequilibrium. Two had recurrences associated with childbirth. Five patients had recurrences associated with postrecovery head trauma (see Table 1). The follow-up in this group of 33 patients ranged from 18 months to 7 years.

Discussion

Perilymphatic fistulas must be considered in the differential diagnosis of persistent vertigo following head trauma. Healy[16] emphasized that "Otologic consultation should be sought in all cases so that appropriate treatment plans may be developed." A thorough otologic evaluation is certainly indicated in all such patients. It has been our practice to wait at least three months after the trauma before considering a surgical procedure in patients who present with vertigo without hearing loss. Spontaneous resolution of the vertigo with healing of the fistula can occur during this time. We have seen several patients whose symptoms have continued to diminish after three months and in those patients we advised continued observation. The great

majority do not show improvement after the three-month period of observation and surgical treatment is therefore recommended. The presence of a hearing loss makes earlier surgical intervention advisable to provide the best chance of reversing the hearing loss. The availability of a benign surgical procedure to relieve the vertigo and reverse hearing loss in these patients is certainly an improvement over the previous management of prolonged observation. Patients who are afflicted with vertigo and hearing loss after head trauma thus may have a pathologic disorder that is identifiable, surgically accessible and curable in a high percentage of cases.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Immunotherapy for Cancer

QUESTION:

In the treatment of cancer, is the following regimen of "immunotherapy" accepted practice: bacille Calmette-Guérin (BCG) titrated with purified protein derivative (PPD) response; autogenous vaccines made from progenitor cryptocides; purified antigen; custom formula made from sheep spleen extract; injections of gamma globulin, cyanocobalamin (vitamin B_{12}) and liver extracts, and megavitamin therapy?

OPINION:

In the opinion of the Scientific Advisory Panel on Internal Medicine, the following regimen of immunotherapy for the treatment of cancer is not considered accepted medical practice: bacille Calmette-Guérin (BCG) vaccine titrated with purified protein derivative (PPD) response; autogenous vaccines made from progenitor cryptocides; purified antigen; custom formula made from sheep spleen extract; injections of gamma globulin, cyanocobalamin (vitamin B_{12}) and liver extracts, and megavitamin therapy.

This regimen is unproved scientifically and the panel members do not condone its use.

Surgical Procedures in Nonagenarians

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During the hospital course of 225 nonagenarian patients who underwent 285 major operations—80% on the general, vascular, orthopedic and urologic services—overall morbidity was 37% and mortality 7.5%. The 100 emergency operations were associated with a higher morbidity and mortality rate. Nonsurvivors were more likely to have associated cardiac or cerebral medical conditions, higher utilization of intraoperative invasive hemodynamic monitoring and greater use of surgical intensive care units. Compared with all surgical patients, the nonagenarians were admitted twice as often to the surgical intensive care unit, required twice the number of hospital days, underwent intraoperative hemodynamic monitoring twice as frequently and incurred 200% greater hospital charges. We conclude that with careful evaluation and management, a nonagenarian patient presenting with a surgical condition can safely undergo necessary operative procedures.

(Michel SL, Stevens L, Amodeo P, et al: Surgical procedures in nonagenarians. West J Med 1984 Jul; 141:61-63)

Surgical intervention in an elderly patient has been the subject of many reviews, but nonagenarians as a class have received scant attention.[1] The landmark age of 90 years still evokes awe and wonderment in our society; we felt it worthwhile to study whether patients of this age and older can successfully withstand major surgical procedures. In this review we analyze our experience with 225 surgical patients aged 90 years and older admitted to the surgical service during a 3½-year period.

Patients and Methods

We reviewed 388 inpatient hospital records, analyzing operative procedures and postoperative courses in 225 nonagenarian patients who had undergone 285 major operations. The patient records were analyzed for the following factors: age, sex, surgical diagnosis, operative procedure, designation as an emergency procedure, anesthetic risk classification, duration and type of anesthesia, associated medical problems, use and type of intraoperative invasive hemodynamic monitoring, intraoperative complications, in-hospital morbidity and mortality, surgical intensive care unit use and length of preoperative and postoperative stay.

Coding of diagnosis and procedures was in accordance with terminology in the *International Classification of Diseases.*[2]

Results

The age range of patients in this study was 90 to 102 years, with an average age for both men and women of 92.1 years. Men comprised 42% of the group, women 58%.

Table 1 depicts the major surgical services to which these patients were admitted. Orthopedics accounted for the largest group, both in percent of operations (33%) and percent of emergencies (52%). The urologic and general surgical services were next in frequency of admissions, with the remainder scattered among other surgical specialties.

Table 2 shows the disease categories for which operations were done.

Hospital Care

Nonagenarian patients constituted 1.3% of all admissions to the noncardiac surgical intensive care units, where their average length of stay was 2.8 days. The average hospital stay for this group was 16.9 days, in contrast to the length of stay for all patients, which averaged 7.2 days. The average patient charge for the nonagenarians was $15,575; for all surgical patients it

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was $5,400. The total cost for the group of 225 nonagenarians was in excess of $3.5 million.

Anesthesia

Classification of anesthetic risk was according to the standardized criteria of the American Society of Anesthesiologists. None of these patients was in the class I or most favorable group. The outcome according to class of anesthetic risk is shown in Table 3.

The most common anesthetic technique was general anesthesia (47%); spinal or epidural anesthesia accounted for 28.9% of anesthetics administered. The remainder consisted of 24.2% of patients operated on under local anesthesia. The average duration of anesthesia was two hours.

Hemodynamic Monitoring

Monitoring by arterial line or Swan-Ganz catheter (or both) was not as frequent as might be expected, either during operation or postoperatively. Only a third of this group had invasive hemodynamic monitoring. As might be expected, hemodynamic monitoring was most frequent in the nonsurvivors (80%) because these were the most critically ill subset of the nonagenarians.

Morbidity and Mortality

The overall morbidity and mortality statistics for those patients in three major specialities are shown in Table 4. Nearly a third of patients undergoing elective operation had some complication; over half of the patients undergoing emergency operation had a major complication. The operative mortality for the entire group was 7.5%. As might be expected, it was twice this number for emergency procedures.

TABLE 1.—*285 Operations by Specialty in 225 Nonagenarians*

Specialty	Percent of Operations	Percent of Emergencies*
Orthopedics	33	52
Urology	21	2
General	17	24
Thoracic	11	8
Vascular	9	10
Eye	4	1
Other	5	3

*N = 100

TABLE 2.—*Operations in Nonagenarians by Disease Category*

Disease Category	Number of Operations*	
Geriatric		
Heart block	32	
Arteriosclerosis	30	
Benign prostatic hypertrophy	25	
Cataract	9	
TOTAL	96	(33%)
Trauma		
Hip fractures	84	
Other	10	
TOTAL	94	(32%)
Natural Disease		
Hernia	16	
Bladder/urethra	13	
Biliary	4	
Small bowel obstruction	4	
Peptic ulcer	4	
Colon	3	
Miscellaneous	10	
TOTAL	54	(19%)
Neoplasm		
Bladder	13	
Prostate	8	
Colon	8	
Breast	6	
Skin	4	
Other	9	
TOTAL	48	(16%)

*7 minor operations are included.

Discussion

Longevity in Biblical times was described thus in the 90th Psalm: "The days of our years are threescore years and ten; and if by reason of strength they be fourscore years, yet is their strength labour and sorrow . . ." In 1980 the life expectancy for men was 70, and for women 77. In that census year, 4% of the US population (9.4 million) was aged 75 years and older; in the year 2000, 5% (13.5 million) of the population will consist of people 75 years and older.[3] No separate figures are available for the group we are

TABLE 3.—*Survival According to Anesthetic Risk*

American Society of Anesthesiologists Class	Survivors Percent	Nonsurvivors Percent
I*	0	0
II	7.7	0
III	46.3	31.8
IV	45.3	54.6
V	0.7	13.6

*Class 1 represents the lowest risk.

TABLE 4.—*Morbidity and Mortality in Three Major Specialties*

Specialty	Entire Series		Elective Operations		Emergency Operations	
	Morbidity Percent	Mortality Percent	Morbidity Percent	Mortality Percent	Morbidity Percent	Mortality Percent
Orthopedic	56	9	59	9	54	10
General	43	12	33	7	54	17
Vascular	28	16	27	0	30	40
Total Morbidity for Series	37.0%					
Total Mortality for Series	7.5%					

discussing, namely those aged 90 and older. Surely the number must be small, very probably a fraction of 1%.

Health care for the aged is an issue of increasing concern and complexity.[4-9] The 11% of the population older than 65 years is responsible for 26% of all days of care in community hospitals and a third of all health care expenditures. The hospital admission rate for persons older than 75 years is 54% higher than that of the group between 65 and 74 years. Hospital expenditures for the population older than 65 years is 3½ times the rate for persons younger than 65 years.

This then is the general picture of American health care in the aged in this decade. What conclusions can we draw about the rare nonagenarian who undergoes an operation? The conclusion is obvious that this group can withstand an operation at a respectable mortality rate. The mortality rate for those aged 90 and older in this series (7.5%) is practically identical with that quoted for octogenarians by Reiss and co-workers.[10] The life expectancy for nonagenarians is three additional years of life, as compared with that for octogenarians, which is five years.

Other reports of surgical experience in the elderly have focused on malignant diseases,[11,12] gastrointestinal operations,[13] hip fractures,[14] inguinal herniorrhaphy,[15] breast cancer,[16] abdominal aortic aneurysm,[17] colorectal tumors,[18] head and neck tumors[19,20] and specific details of intraoperative care.[21-23] More comprehensive reviews, similar in scope to the present series, serve to put our results in context with other authors' experience.[1,11,24-28]

Our study specifically identifies the frequent utilization by these nonagenarian patients of the surgical intensive care unit and their substantial length of stay in the hospital, two factors not reported in the other referenced series. It is helpful to be aware of the distribution of these elderly patients among the surgical specialties, the types of illnesses with which they present, their relative cumulative use of such resources as intensive care unit beds and operating rooms and the total cost of their care.

A surgeon managing these very elderly patients must recognize the physiologic alterations that occur in all organ systems as part of the aging process. Compared with a young adult (age 30), an elderly person (age 75) has remaining only 43% of maximum breathing capacity, 69% of glomerular filtration rate, 70% of cardiac output and 84% of basal metabolic rate.[29] In addition to these decreases in major organ system functions, hepatic metabolism is altered, resulting in a tendency for hyperglycemia to develop and causing changes in the effectiveness of standard doses of commonly used drugs.[30] These age-related physiologic changes cause nonagenarian patients to be extremely intolerant of any injudicious clinical assessment or management of volume depletion, fluid overload, pulmonary support, renal perfusion or metabolic abnormality, as reported by Del Guercio and Cohn.[23] Surgeons must carefully evaluate and prepare nonagenarians who present with a surgical condition. They must recognize and treat coexistent medical disorders and monitor hemodynamic and other vital functions during and after operation.

This study shows that patients 20 to 30 years older than previously described high-risk elderly surgical patients can safely undergo necessary surgical procedures. These nonagenarian patients, like the "one-hoss shay,"[31] have not only lived a long life but still possess sufficient resilience to tolerate major operations, though they can deteriorate quickly when one or more serious complications occur in the postoperative period.

". . . [A]nd that's the reason, beyond a doubt, that a chaise *breaks down,* but doesn't *wear out.*"[31]

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Polymyalgia Rheumatica and Giant Cell Arteritis

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Polymyalgia rheumatica is a relatively common syndrome of older patients, mostly white, manifested by aching and morning stiffness of the pelvic and shoulder girdles and accompanied by a rapid erythrocyte sedimentation rate. The symptoms are due to a synovitis, which is mild, nondestructive and very responsive to low-dose steroid treatment, which may need to be continued for several years. Temporal arteritis, which may accompany polymyalgia, can present as headache, loss of vision, diplopia or jaw claudication. To suppress arterial inflammation and preserve vision, administration of prednisone, 50 mg a day for one month, is recommended, following which the dose is tapered according to the symptoms, not the sedimentation rate.

(Healey LA, Wilske KR: Polymyalgia rheumatica and giant cell arteritis [Medical Progress]. West J Med 1984 Jul; 141:64-67)

It was not until 1963 that the first report of a case of polymyalgia rheumatica appeared in an American medical journal.[1] Despite reports of the syndrome and its association with temporal arteritis coming from Great Britain and Scandinavia and Horton's description of temporal arteritis at the Mayo Clinic in 1932, polymyalgia was not being diagnosed. In the two decades since 1963, these syndromes have become well known and readily recognized. In retrospect, one wonders whether there has been a real change in incidence or, to our chagrin, whether physicians did not recognize the diagnosis because we were not sensitized to look for it. In 1978 we reviewed what was known and had been written about polymyalgia rheumatica and giant cell (temporal) arteritis.[2] In this article we focus on recent information on diagnosis, duration of disease and treatment that has appeared since 1978. We also discuss hypotheses of etiology and pathophysiology and the relation between polymyalgia and temporal arteritis.

Polymyalgia Rheumatica

Participants at a recent workshop agreed on a definition of polymyalgia rheumatica as a clinical syndrome of unknown cause that rarely occurs in persons younger than 50 years and is characterized by aching and morning stiffness in the torso and proximal limbs with evidence of systemic inflammation that may be manifest as malaise, weight loss, low-grade fever, anemia or an increased sedimentation rate.

Recognizing that criteria for classification to be used in studies of groups are quite different from those used to diagnose an individual case, the workshop also drew up the following criteria for use in clinical studies:

- Age of onset 50 years or older,
- Bilateral aching and morning stiffness in at least two of the following three areas—shoulders and proximal arms, hips and proximal thighs and neck and torso,
- Symptoms present for at least a month and
- A Westergren erythrocyte sedimentation rate of 45 mm or more in the first hour or an equivalent change in another measure of inflammation.

It is evident that these criteria are not specific and can only be applied when other diseases such as rheumatoid arthritis, lupus, polymyositis, infection and cancer are excluded.

In diagnosing polymyalgia, a sedimentation rate approaching 100 mm an hour provides dramatic confirmation, but the diagnosis really depends on a patient's history, as indicated by the statement that the disease can be recognized over the telephone. Older patients previously well or coping with the aches of osteoarthritis describe a distinct change in symptoms. Pain may

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or may not be severe, but morning stiffness is striking. Patients relate how difficult it is to rise from bed in the morning or get out of a car after a long drive. Despite these severe symptoms, there is a paucity of objective findings; most patients show little other than pain on moving shoulders and hips and tenderness to palpation. Radiographs show only the changes of age and, apart from mild anemia of varying degree and the sedimentation rate, the results of laboratory tests are all normal. What then is the cause of the pain and particularly the stiffness?

Evidence is accumulating to indicate that it is a synovitis. Scintigrams done with sodium pertechnetate To 99m showed an increased uptake primarily in the shoulders but to a lesser degree in knees and wrists.[3] Arthroscopic examination of the shoulder joint in 19 patients with polymyalgia rheumatica has shown synovitis manifest by erythema and edema; effusions were present in 17. In contrast, arthroscopy in ten patients with nonspecific shoulder pain showed no abnormalities. Histologic examination of tissue removed at arthroscopy in the patients who had polymyalgia showed a mild inflammation with perivascular infiltration by lymphocytes and rare polymorphonuclear leukocytes. No fibrin deposition or vasculitis was identified and the changes were quite different from those of rheumatoid synovitis.[4]

In 246 of our patients with polymyalgia who were followed up for more than 17 years, clinical manifestations of synovitis appeared in 77 (12 of these 77 also had giant cell arteritis as seen on biopsy specimens).[5] Knee effusions and swelling of wrists, often with carpal tunnel syndrome, were encountered most frequently. Effusions were found in 37 patients and fluid was aspirated in 14. Some effusions were sizable; 30 to 150 ml was removed and the counts ranged from 5,900 to 21,000 leukocytes per μl, a leukocyte response indicative of inflammatory synovitis. No crystals were present.

Synovitis in cases of polymyalgia is relatively mild, confined to several joints and usually appears at the onset of the disease or when steroid doses are rapidly tapered. It is readily treated and does not cause joint deformity or radiographic change.

Because polymyalgia appears to be a synovitis that can produce swelling of knees and wrists, it is often difficult to distinguish from the onset of rheumatoid arthritis, particularly in older patients in whom the results of a rheumatoid factor test are frequently negative, and the disease may involve proximal joints rather than more characteristic small joints of the hands and feet. In some such patients, only the subsequent clinical course will reveal the true diagnosis.

An epidemiologic survey of Olmsted County, Minnesota, showed an average annual incidence rate of 53.7 per 100,000 population 50 years of age or older, a figure that approaches that of rheumatoid arthritis in the same age group.[6] Of the 97 patients seen over a ten-year period, all were white and two thirds were women. Steroids were given to 54 of these patients and the rest, considered to have mild disease, were treated satisfactorily with aspirin or other nonsteroidal drugs. The mean duration of the disease was 11 months (range, 2 to 54 months). Patients receiving nonsteroidal treatment had a shorter course, but this may indicate milder disease rather than a prolongation of the illness by steroids.

All of our 246 patients were treated with low-dose steroids (initial dose, 15 mg daily; maintenance dose, 5 mg) and did well. In our patients, the disease followed a longer course. For example, after 24 months 70% of the patients were still taking prednisone.[5] The duration of disease is unpredictable. With each successive year, more patients were able to stop taking the prednisone without a recurrence, but for a few it was necessary to continue for as long as ten years. Despite this prolonged course, there was no joint damage and patients remained well on the low, well-tolerated steroid dose. A prolonged course also was true of cases reported from Scandinavia.[7]

In each reported series there were a few patients with polymyalgia who do not have the very rapid sedimentation rate. When encountering such patients, it is difficult to be certain of the diagnosis, but it can be made if the following conditions are met:

- A history of a clearly recognized onset of new symptoms,
- Pronounced morning stiffness of at least an hour,
- Exclusion of other diagnoses and
- Complete relief of symptoms within a week by administering low-dose prednisone.

Relation of Polymyalgia Rheumatica and Giant Cell Arteritis

It is well recognized that polymyalgia may at times be a manifestation of giant cell arteritis. The two syndromes have been noted in the same patient either concurrently or at different times, and arteritis has been shown on biopsy specimens taken of asymptomatic temporal arteries in polymyalgia patients. How often polymyalgia is an indication of arteritis is still unanswered. The incidence of polymyalgia in various reported series of patients with giant cell arteritis varies from 48%[8] to 90%.[7] In our experience, it has been 60%.[9]

Conversely, in the series of cases of polymyalgia rheumatica the incidence of proved arteritis was 15%.[6] In our series, 22% had clinical or biopsy evidence of arteritis.[5] These figures are only estimates because of the possibility of error in two different ways—not every patient with polymyalgia had a biopsy and, as mentioned, arteritis has been found in asymptomatic arteries of polymyalgia patients. On the other hand, a biopsy specimen may fail to show arteritis in patients in whom the diagnosis was certain clinically—that is, those who had a sudden loss of vision—or in whom a later biopsy specimen showed the lesion. The report of Jones and Hazleman[10] highlights the difficulty in that, of 85 patients with polymyalgia rheumatica, giant cell arteritis

later developed in three in whom no abnormalities were found on a biopsy specimen and the biopsy specimens showed giant cell arteritis in four patients who never had clinical evidence of arteritis. A biopsy cannot be the absolute standard as the arteritis is randomly distributed and areas of inflammation are interspersed with normal vessel.[11]

The association of polymyalgia and giant cell arteritis seems much higher in the Scandinavian series, and investigators have followed the view of Hamrin who recommended the name polymyalgia arteritica, suggesting that the two are one and the same. In a large series from Sweden, however, biopsy specimens showed giant cell arteritis in 90% of patients with clinical temporal arteritis but in only 31% of 67 patients who had only polymyalgia rheumatica.[7] The clinical observation that most persuades that polymyalgia rheumatica is not always a manifestation of giant cell arteritis is that in most patients followed up for more than ten years clinical arteritis never develops.[5,6] This experience is the basis for the recommendation that patients who have only polymyalgia rheumatica with no symptoms of headache, diplopia, jaw claudication or loss of vision to suggest cranial involvement not have a temporal artery biopsy and not receive high-dose steroid but that they be treated with a low dose to relieve their rheumatic symptoms.

Temporal Arteritis

Temporal arteritis is also known as cranial arteritis and giant cell arteritis, each name indicating some aspect of disease. In a survey of Olmsted County, 42 patients were identified during a 25-year period, an average annual incidence rate of 11.7 per 100,000 population aged 50 years or older.[8] While biopsy-proved temporal arteritis has been found in blacks and Asians, it is overwhelmingly a disease of whites. Familial occurrence is no greater than might be expected by chance alone. Studies have shown an association with the human leukocyte antigens Cw3, DR3 and DR4 (L. A. Healey, MD, Kenneth R. Wilske, MD, and J. A. Hansen, MD, unpublished observations).

It is convenient to separate the clinical manifestations of giant cell arteritis into generalized symptoms that are characteristic of a systemic inflammatory disease and localized syndromes that depend on the particular vessel involved. Systemic manifestations include a rapid sedimentation rate, anemia, fever, weight loss, anorexia, malaise, abnormalities on liver function tests, particularly the alkaline phosphatase, and polymyalgia rheumatica. In some patients, one or more of the systemic manifestations may be the presenting or predominant complaint, posing such well-known diagnostic puzzles as fever of unknown origin or unexplained anemia or suggesting an occult malignant disease. The fever may be hectic, ranging from 37.4°C to 39.4°C (99°F to 103°F) with frequent night sweats but no shaking chills. A nonspecific illness in an older patient who has anorexia, malaise, weight loss, anemia and abnormal liver function strongly suggests cancer. In such patients, a very rapid sedimentation rate suggests the diagnosis of giant cell arteritis, which can be confirmed by temporal artery biopsy. Attention has been called to these presentations with the terms occult giant cell arteritis[12] and masked giant cell arteritis.[13]

Local manifestations depend on the particular artery involved. They include classic headache—which led to the name temporal arteritis—and sudden unilateral blindness from occlusion of posterior ciliary branches of the ophthalmic artery. Transient diplopia may be due to paralysis of an extraocular muscle when its nutrient vessels are involved, and the pathognomonic pain with chewing (jaw claudication) signals arteritis of the facial artery. Giant cell arteritis may involve the aorta and its major branches; a Mayo Clinic study showed such large artery involvement in 9% of 248 patients,[11] but the inflammation does have a predilection for the cranial arteries.

Both the anatomic distribution and the histologic appearance of the lesions focus attention on the internal elastic lamina as a key tissue. Based on postmortem examination in 12 cases, Wilkinson and Russell noted a correlation between a susceptibility to arteritis and the amount of elastic tissue in the media of the arteries of the head and neck. This was notably exemplified by severe inflammation of vertebral and internal carotid artery vessels to the point of dural perforation wherein there is a significant reduction in elastic tissue of vessel walls. This was also true for the ophthalmic and posterior ciliary arteries, which are involved by the disease much more often than the central retinal artery, which loses its elastic tissue as it penetrates the optic nerve sheath.[14] This theory is attractive in that it would provide an explanation for a relative sparing of intracranial arteries, coronary arteries and the arterioles of kidney and lung. Both clinically and pathologically these are infrequently involved in temporal arteritis in contrast to cases of polyarteritis nodosa. In the Olmsted County survey temporal arteritis had no effect on life expectancy and the patients had no more coronary artery or cerebrovascular disease than the rest of the population of the same age.[8]

The pattern of artery involvement and the histologic appearance, particularly that seen by electron microscopy, suggest that the elastic tissue in some way may be initiating a cell-mediated immune response. Fragments of elastic tissue are surrounded by histiocytes, giant cells, monocytes and lymphocytes. Most of the lymphocytes have been identified by monoclonal antibody reactivity as T cells of the helper/inducer subset.[15] However, tests of cellular immunity have shown no consistent abnormality and extracts of elastin have failed to stimulate lymphocytes.[16]

Immunoglobulin and complement deposition adjacent to the elastic lamina, circulating immune complexes, and the response of symptoms to steroid suggest that antibody interactions may be important. Elevated levels of immune complexes have been found in the

serum of patients who have active untreated disease, both temporal arteritis and polymyalgia.[17] Measurements of von Willebrand factor, a marker of vascular endothelial cell damage, have given similar results. It is still uncertain whether these observations are of primary pathophysiologic importance or whether they are secondary events.

Treatment

As with polymyalgia rheumatica, symptoms of temporal arteritis are readily reversed by steroid therapy. The choice of dose is predicated on one consideration, prevention of irreversible blindness. Low doses do not protect against loss of vision. Accordingly, the recommended dose is at least 50 mg of prednisone (or equivalent) a day for one month before beginning a gradual taper. In our experience, this schedule has been effective in suppressing the manifestations of inflammation and preventing later occurrences. The dose is then gradually tapered over six months to a daily maintenance dose of 5 to 7.5 mg a day. The steroid dose is tapered according to a patient's symptoms rather than sedimentation rate. Initially the sedimentation rate is a good indicator of response, but in the subsequent course a rise in the sedimentation rate does not parallel a flare of arteritis. Attempts to produce a normal sedimentation rate invariably result in steroid toxicity, most often osteoporosis and vertebral collapse. Symptoms provide a better guide to steroid dosage.

This recommendation is based on the observation that the risk of blindness is greatest in the early stages of the disease, thus the high dose is continued for one month. A small minority of patients have lost vision even while on steroid treatment, but this has happened within two weeks of starting the medication regimen. Exacerbations later in the course when steroid has been discontinued too soon have been those of polymyalgia, not arteritis.

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More on Polymyalgia Rheumatica and Giant Cell Arteritis

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Elsewhere in this issue Healey and Wilske review recent data on polymyalgia rheumatica and giant cell arteritis based on their own extensive experience and reports in the literature. They point out that even though Horton had described cases of temporal arteritis as early as 1932 and that the European literature reported cases of polymyalgia rheumatica under several different names, both conditions were considered uncommon in this country before the mid 1960s. They raise the question whether these conditions were merely poorly recognized in the United States in earlier years or whether there has been a change in the frequency of these diseases to account for the high incidence rates that have been described in some recent surveys.

In the Olmsted County, Minnesota, epidemiologic study of giant cell arteritis, incidence rates could be calculated over time and the change documented.[1] The rates increased more than three times from 5.1 per 100,000 persons older than 50 years of age in the first decade surveyed (1950 to 1959) to 17.4 cases per 100,000 persons in the last five years of the study (1970 to 1974). The prevalence of active and resolved cases at the beginning of 1975 was 133 per 100,000, that is, about one case in every 750 persons older than 50 years. Somewhat similarly, the prevalence of polymyalgia rheumatica increased 22% in the second five-year segment (1975 to 1979) of the ten-year Olmsted County study.[2] An estimated prevalence of active and resolved cases of polymyalgia rheumatica at the beginning of 1980 was about 500 per 100,000 persons older than 50 years, or 1 person in 200.

Healey and Wilske note some recent descriptions of the diverse guises in which giant cell arteritis may present, such as depression, anemia and fever of unknown origin with shaking chills, which may not directly suggest the underlying nature of the disease.[3] Such reports aid in identifying occult cases. In addition, the characteristics of aching and morning stiffness of polymyalgia rheumatica are also better recognized. Although objective findings are not prominent in cases of polymyalgia rheumatica, careful examination may show, in addition to small knee effusions, slight swelling or tenderness of several other joints and limitation of active and passive motion of the shoulders and hips. In severe cases of longer duration, disuse muscle atrophy of the shoulders may become clearly evident. Radiographic changes of joint damage have been seen occasionally, also supporting the idea that synovitis is an important cause of the musculoskeletal pains.[4] In fact, in a small number of patients persistent synovitis eventually may permit a diagnosis of seronegative rheumatoid arthritis.

It is clear that cases of polymyalgia rheumatica did occur before the 1960s. At our own institution, for example, polymyalgia rheumatica went under the name of "secondary fibrositis" and was considered a moderately common process but it was not studied thoroughly.

The final answers on the questions of changing incidence or better recognition remain to be given, but I suspect that much of the "change" is better awareness nowadays of both conditions, plus a predisposition toward them of certain populations. If improved recognition is the cause of the increasing incidence rates, the rates should begin to level off as maximum awareness is reached. A recent occurrence at our institution suggests that a good level of awareness by many doctors is being approached. An internist member of the Infectious Disease Division was evaluating a patient with a fever of unknown origin and asked a general surgeon to see the patient with a view toward a possible abdominal exploration to further investigate the cause of the fever. The surgeon looked over the data and asked the internist whether he had thought of the possibility of giant cell arteritis even though no headache or visual symptoms were present, and would consider a temporal artery biopsy before going to the abdominal exploration!

Other factors, such as genetic or even climatic, may also influence the incidence of these conditions. As has been pointed out, giant cell arteritis is most common in whites. A relationship with the antigen HLA-DR4 has been noted by several authors. Identical twins and multiple family members with these conditions have

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also been reported, but the meaning of this has yet to be completely determined.

Smith, Fidler and Pinals studied the epidemiology of giant cell arteritis in Shelby County, Tennessee, an urban population in South Central United States.[5] Over a ten-year period (1971 to 1980), 26 cases were identified, producing an average annual incidence of 1.58 per 100,000 persons aged 50 years and older. The incidence was seven times greater in whites than in blacks. But the overall incidence was considerably lower than recorded in Olmsted County[2] and also in Scotland[6] and Sweden.[7] The authors felt that the differences between their findings and those of others could be accounted for only in part by racial distribution. Assuming good case ascertainment by Smith and coworkers, a potential role for climate or other environmental influences needs to be considered. Similar studies in other southern locations or other geographic areas should be carried out to place the various studies in perspective and to search for factors that may have etiologic significance.

As pointed out by Healey and Wilske, the artery lesions appear to focus on elastic tissue, but no direct evidence of an immunologic reaction to elastic tissue has been obtained. In addition to the work cited by Healey and Wilske, we have looked for antibodies to elastic tissue in serum specimens from patients with giant cell arteritis (J. M. Peterson and G. G. Hunder, MD, unpublished observations). An assay was used in which patients' serum was mixed with purified, denatured, finely particulate and insoluble human aortic elastin. After adding the patient serum, the elastin was washed and mixed with ^{131}I-labelled staphylococcal A protein to detect IgG antielastin antibodies. No antibodies were found in serum specimens from 15 patients, though one of ten serum specimens from patients with lupus erythematosus did have elevated antibody titers, as did serum from guinea pigs that were immunized against human elastin. A search for antibodies to native elastin might yield different results.

It is to be hoped that improved methods of diagnosis will be developed to help determine whether patients with somewhat similar, but not typical, symptoms also have these diseases. Use of the workshop standards for defining polymyalgia rheumatica should help make study results more comparable from one center to another, especially since no diagnostic test for polymyalgia rheumatica is available. The fact that heavy emphasis is placed on the erythrocyte sedimentation rate in the recognition of polymyalgia rheumatica indicates a need for better tests. Furthermore, it should be remembered that polymyalgia rheumatica as well as giant cell arteritis may occur in association with a normal or near-normal erythrocyte sedimentation rate. The frequency of this is not known but probably occurs in about 1% of those with giant cell arteritis and slightly more often in cases of polymyalgia rheumatica. The availability of baseline erythrocyte sedimentation rates before a patient became ill may help evaluate current tests.[2] Other acute-phase reactant blood proteins such as C-reactive protein, fibrinogen, α_2-globulins and the like have been used to follow patients but have not been shown to be significantly better than the erythrocyte sedimentation rate in this regard. Nevertheless, these tests can be used in conjunction with the sedimentation rate to help evaluate the status of patients.

On the other hand, in giant cell arteritis a positive finding on a temporal artery biopsy specimen is diagnostic. Opinions on the clinical usefulness of doing temporal artery biopsies when giant cell arteritis is suspected have varied considerably. Wilske and Healey point out instances of patients who had no abnormalities on a temporal artery biopsy but in whom symptoms of giant cell arteritis later developed and, conversely, patients with polymyalgia rheumatica who had no symptoms of arteritis but who had a biopsy in which the specimen showed giant cell arteritis. Other authors have suggested that when the diagnosis seems clear on a clinical basis, a biopsy is superfluous, and in cases where the clinical picture is obscure, a patient may be treated despite the absence of abnormalities on a biopsy. Therefore, the argument sometimes goes, biopsies are not usually required. In addition, a patient may need a superficial temporal-middle cerebral artery bypass operation at some time in the future and the temporal artery should be saved in anticipation.

Now, two studies have evaluated the efficacy of temporal artery biopsy. In one, 193 temporal artery biopsies were done over the 10-year period, 1968 to 1978.[8] In 28, the biopsy specimens showed arteritis. Follow-up information was available for at least two years after the biopsy in 91 of these, including the 28 with positive findings and 63 with negative findings. Only three cases in which results of a biopsy were negative (5%) were diagnosed as temporal arteritis. One of the patients died five months after the biopsy and was found to have temporal arteritis at autopsy. The other two patients were felt to have temporal arteritis clinically at the time of biopsy. No biopsy-related complications were noted immediately or found in the follow-up. The authors suggested that a biopsy may be done of the frontal branch of the superficial temporal artery if there is concern about the need for a temporal-middle cerebral artery bypass operation in the future, as the parietal branch is usually preferred for this procedure. None of their patients were noted to need such treatment.

In the second study, all 134 residents of Olmsted County who had temporal artery biopsies over the 15-year period (1965 to 1980) were followed.[9] Initially the biopsy specimens showed positive findings in 46 cases and negative in 88. No complications from the biopsy procedure were observed and in none has a question yet come up about the need for a bypass surgical procedure. There was a close similarity between biopsy-positive and biopsy-negative groups in overall presenting clinical features, with almost equal frequencies of polymyalgia rheumatica, fever, headaches and visual disturbances including blindness. Two findings, however—jaw claudication and clinical ab-

normalities of a temporal artery—were significantly more common in patients in whom the biopsy specimen showed giant cell arteritis. A history of jaw pain or claudication was found in 54% of the biopsy-positive group, but in only 3% of the patients who had normal biopsy results. A clinically abnormal temporal artery was present in 67% of those in whom biopsy results were positive, which was more than twice as common as in those in whom abnormalities were found on biopsy. Jaw pain or abnormal temporal arteries, or both, were present in 78% of those with positive biopsy results. Over a median follow-up of 70 months, only 8 of the 88 biopsy-negative patients had clinical courses requiring long-term, high-dose corticosteroid therapy for giant cell arteritis. In these eight, a diagnosis of giant cell arteritis was made during follow-up on the basis of an additional temporal artery biopsy, autopsy examination, angiographic studies or the development of convincing clinical evidence. To put these findings in terms of efficacy of biopsy, it could be stated that the initial temporal artery biopsy correctly predicted the subsequent need for corticosteroid therapy in 94% of cases (46 plus 80/134). A temporal artery biopsy that showed no abnormalities accurately predicted that high-dose corticosteroid therapy was not needed in 91% (80/88). These figures compare well with most tests available today and indicate that temporal artery biopsy should be done before patients are committed to high-dose, long-term corticosteroid therapy. The high predictive value of findings on a temporal artery biopsy in this study may be due in part to our practice of taking a large biopsy specimen and frequently carrying out bilateral biopsies when examination of frozen sections of the first side shows no abnormalities. In this study, 15 of the 46 initially positive biopsies were bilateral and 49 of the 88 negative biopsies were bilateral. If a temporal artery is clearly abnormal clinically, only a small segment need be removed for histologic examination; but if the arteries are not clearly abnormal a larger segment, 3 to 6 cm in length of one or of both sides, should be taken for examination because the arteritis frequently does not affect all portions of the artery and identification of affected areas may be found only after an examination of many sections.

The question of whether to do a temporal artery biopsy in a patient with polymyalgia rheumatica who has no vascular-related symptoms or signs may be more difficult because, as pointed out, some have arteritis. On the assumption that arteritis is unlikely, such patients tend to be treated with nonsteroidal anti-inflammatory drugs or low doses of corticosteroids, which would ameliorate musculoskeletal pain and cause fewer drug side effects but might not prevent vascular complications should giant cell arteritis be present. My clinical experience with these cases suggests that patients with milder disease, especially early in the course of the illness, or those whose symptoms have been present for longer than a year may be carefully followed without a biopsy. The chance of vascular complications in such patients is quite low though not accurately known. An estimate may be roughly calculated by considering that temporal artery biopsy will show giant cell arteritis in about 15% to 20% of patients with polymyalgia rheumatica without symptoms or signs of giant cell arteritis. Of those with arteritis, vascular complications might occur in perhaps 20% to 40% if not treated. Thus, patients with polymyalgia rheumatica lacking findings of giant cell arteritis might have vascular complications in a frequency of 3% to 8%. If such patients are treated with low doses of corticosteroids and all symptoms resolve and the laboratory tests return to normal, vascular occlusions or ruptures probably will not occur regardless of the nature of the underlying disease. The problem of not doing a biopsy before treatment arises in interpreting the meaning of a persistently elevated sedimentation rate and only partial resolution of the anemia, though musculoskeletal pains have lessened, after starting therapy at low or moderate corticosteroid doses.

As noted by Healey and Wilske, most patients with giant cell arteritis respond rapidly to corticosteroid treatment. The optimal dose probably differs from patient to patient. Because a chance of irreversible damage from a vascular occlusion or rupture is present, it has been the usual practice to give large initial doses as suggested, even though they may be higher than necessary in some patients. On the opposite side, a small percentage of patients with giant cell arteritis do not respond as readily to corticosteroids, and high doses given over a longer period regularly result in osteoporosis of the spine with compression fractures or other complications. The reason for this occasional lack of response is not apparent and such patients are indistinguishable from responsive patients regarding pretreatment symptoms and histopathologic findings. These cases pose a difficult problem because no other drugs have been shown to be clearly effective in the treatment of this disease. Cyclophosphamide, azathioprine, dapsone and a variety of other medications all have been reported as being useful; however, the experience with these medications is anecdotal and no control studies have been reported. Nevertheless, if pronounced hypercortisonism develops in a patient after several months of high-dose prednisone therapy, consideration can be given to starting one of these drugs such as cyclophosphamide if evidence of clinical activity is obvious.

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Specialty Conference

New Advances in Bone Research

Moderator
HARLAN C. AMSTUTZ, MD

Discussants
ERIC E. JOHNSON, MD; GERALD A. M. FINERMAN, MD; ROY A. MEALS, MD; JOHN R. MORELAND, MD; WILLIAM C. KIM, MD, *and* MARSHALL R. URIST, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine, UCLA School of Medicine, Los Angeles. William M. Pardridge, MD, Associate Professor of Medicine, is Director of Conferences.

In the past 20 years there has been an explosion in developments in the care of musculoskeletal disease. Large segmental defects created by trauma or tumor resections can now be treated with massive allografts. The use of an electrical charge to accelerate bone formation is one of the exciting new developments in orthopedics. Recently developed microvascular surgical techniques enable surgeons to successfully reattach amputated digits and limbs. Equally important are the advances in transfer of vascularized large bone grafts to bridge segmental defects. Total joint replacement has had the greatest impact on the treatment of joint disorders. Although techniques using acrylic fixation have improved, loosening is now the major complication of all long-term acrylic devices. Acrylic-fixed devices have a finite life, deteriorating with time. The hope for the future seems to lie in new methods of fixation using porous ingrowth. One of the most promising adjuncts to bone grafting and potential to enhance ingrowth into porous systems is the use of bone morphogenetic protein. Identification of osteoprogenitor cells and the chemical identification of key elements in a system of osteogenetic stimulation will eventually be clinically available and have far-reaching implications.

The Treatment of Malignant Segmental Defects of Bone—The UCLA Experience

ERIC E. JOHNSON, MD:* The treatment of large segmental skeletal defects is one of the more challenging problems encountered by orthopedic surgeons. Since the late 1800s osseous allograft has been the advocated treatment of large segmental defects that occur from benign or malignant tumors, arthrodesis of joints and repair of traumatic defects. There have been numerous reports in the literature of good to excellent results for the treatment of initially benign tumors and, during the past two decades, of low-grade and high-grade malignant tumors. These techniques have been used at UCLA in combination with doxorubicin hydrochloride and radiation therapy preoperatively and adjuvant chemotherapy postoperatively in attempts to salvage a functioning extremity, control local recurrence and—it is hoped—improve survival.

Allografting began in 1881 when McCewen[1] successfully allografted a defect in a child's humerus. Lexor[2] in 1908 and Inclan in 1942[3] implanted allografts for benign skeletal defects, including osteochondral grafts for joint replacement. As this technique proved to be successful in cases of nonaggressive disease, it was also used in treating low- and high-grade malignant tumors. In 1973 Parrish[4] reported long-term results on 21 patients with benign or low-grade malignant tumors and noted an acceptable success rate. In 1976 and 1982, Mankin and associates[5,6] used allograft in the treatment of malignant or aggressive tumors. Although they noted a significant complication rate, this was acceptable be-

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cause of the technical problems inherent in this type of surgical treatment.

Besides obviating the sacrificing of normal host structures, allografts have certain advantages, including no donor site morbidity and no limit in size, shape or quantity of bone. However, allografting of large defects has several disadvantages, including delayed or incomplete incorporation with normal host bone, fracture or loosening of fixation, infection, possible transfer of disease and extensive laboratory preparation.

As with the transplantation of any tissue, an immunogenic response occurs. Compared with prepared bone, fresh bone allografts stimulate a strong antigenic response. Burchardt and Enneking[7] have shown that freezing (−80°C), freeze-drying or chemosterilizing antigen-extracted autodigested alloimplant ("AAA") bone substantially decreases the antigenicity of a graft. All of the techniques currently used for preserving bone result in a loss of cell viability, but the osseous tissue retains definite biologic potential in regards to stimulating vascular invasion, resorption of old matrix and synthesis of new bone.[8]

The UCLA Medical Center Division of Surgical Oncology, under the direction of Drs T. T. Grant and F. L. Eilber,[9] initially developed a limb salvage protocol consisting of preoperative and postoperative adjuvant chemotherapy, whole limb irradiation and en bloc resection for the treatment of extremity osteosarcoma. Preoperative chemotherapy consists of intra-arterial administration of 30 mg of doxorubicin, which is continuously infused by pump directly into the tumor for 24 hours on each of three consecutive days (Figure 1). Then 350 rads of whole-limb irradiation are given by rapid fractionation for ten days for a total dosage of 3,500 rads. One to two weeks after completing the radiotherapy, surgical resection is done, obtaining a 10-cm proximal margin on all specimens, which is verified by frozen section.

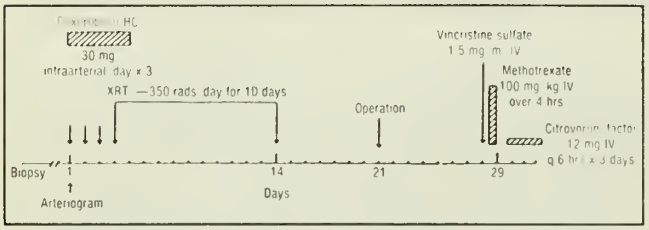

Figure 1.—Preoperative adjuvant chemotherapy and irradiation (XRT) given before resection.

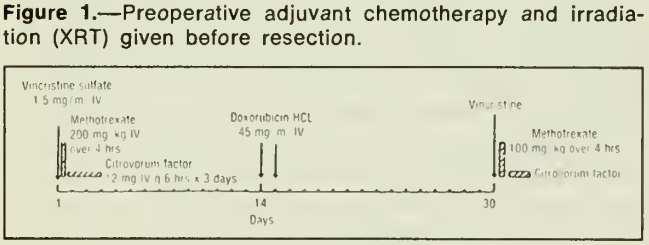

Figure 2.—Postoperative chemotherapeutic regimen.

Postoperative adjuvant chemotherapy is begun two weeks after surgical resection. Doxorubicin is alternated with the combination of vincristine sulfate and methotrexate given intravenously twice a month (Figure 2). Chemotherapy is repeated every two weeks until a maximum dose of doxorubicin of 450 mg per sq m of body surface is achieved. Doxorubicin is then discontinued and methotrexate is given once a month for a year.

The primary goal of this protocol is to permit a functional salvage of the involved extremity by replacing the resected tumor and controlling metastasis and local recurrence. Histologic evaluation of the effectiveness of this protocol shows an average cell viability loss of 98% in all resected tumor specimens.

Between 1975 and 1979, 29 patients with upper and lower extremity osteosarcoma (20 femoral and 9 humeral) refused amputation and underwent resection using the UCLA Limb Salvage Protocol (Table 1). At an average follow-up of 19 months, 12 patients out of 20 with femoral disease survived; at an average follow-up of 2½ years, eight patients out of nine with humeral disease survived.

Initially the freeze-dried or fresh-frozen cadaveric allografts were used in 11 femurs and 7 humeri. One total humeral, one proximal humeral and five distal

TABLE 1.—*Characteristics of 29 Patients With Osteosarcoma Who Underwent the UCLA Limb Salvage Protocol, 1975-1979*

Site	*Sex* ♂	♀	*Average Yrs*	*Survival*	*Average Follow-up*
Femur	12	8	20.2 Range, 12.0-47.2	12/20	19 mos Range, 8.6 mos-3.8 yrs
Humerus	6	3	18.9 Range, 16.0-31.6	8/9	2.5 yrs Range, 7.0 mos-3.4 yrs

TABLE 2.—*Operative Procedures in 29 Patients With Osteosarcoma Who Underwent the UCLA Limb Salvage Protocol, 1975-1979*

Site	*Allograft IM Rod PMMA*	*Giliberty plus Allograft*	*Endoprosthesis*	*Total Femur*	*Arthrodesis*	*Amputation*	*Total Operations*	*Total Patients*
Femur	10	1	6	2	2	3	24	20
	Extensive Resection plus Allograft	*Total Humerus*	*Middle ⅔ Resection plus Allograft*	*Endoprosthesis*	*IM Rod plus Allograft*	*Excision Allograft*	*Total Operations*	*Total Patients*
Humerus	5	1	1	1	1	1	11	9

IM = intramedullary
PMMA = polymethyl methacrylate

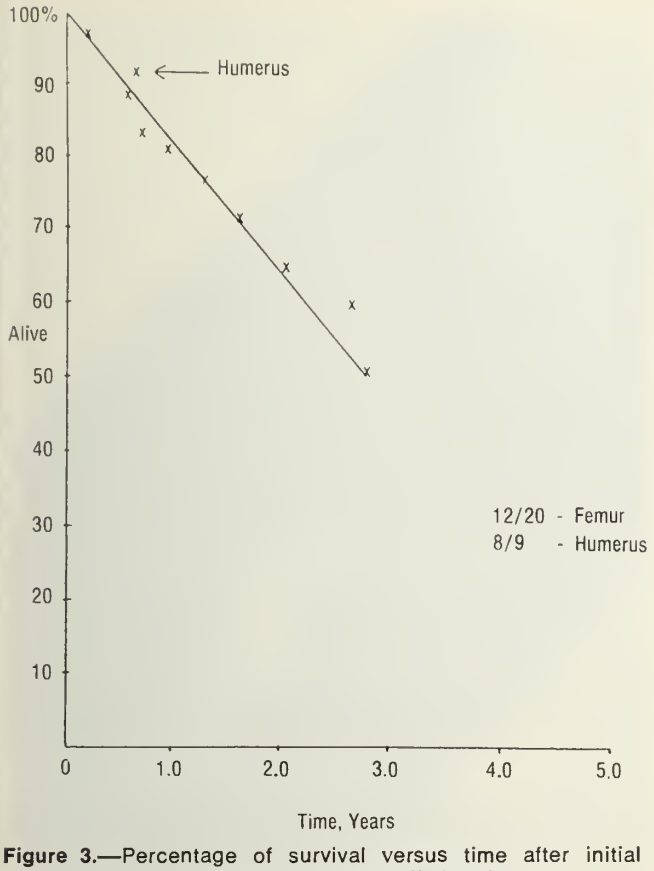

Figure 3.—Percentage of survival versus time after initial operative procedure for osteosarcoma limb salvage.

femoral endoprostheses have been used during the past 1½ years of this study. Two patients underwent resection arthrodesis of the knee, and two patients had total endoprosthetic femoral replacement (Table 2). All allograft replacements failed because of fracture, infection, loosening of fixation and nonincorporation with host bone (the last type of failure is most likely related to soft tissue changes resulting from adjuvant chemotherapy and irradiation). Endoprosthetic replacement also carried the risk of loosening, fatigue fracture and infection; however, follow-up to date of this mode of therapy has not been long enough to evaluate failure rates.

The patients were examined for muscle strength and range of motion, pain with rest and ambulation and evidence of local recurrence. The femoral allografting and endoprosthetic replacements were mainly done for distal femoral disease. Muscle strength was decreased about two grades in the quadriceps and hamstrings and about one grade at the ipsilateral hip. This decrease was related to a combination of the amount of tissue resected and the postoperative irradiation. The lower extremity range of motion was decreased from 25% to 40% at the hip and about 74% in knee flexion as compared with a normal extremity. In the upper extremity, most of the lesions involved the proximal humerus. Because of the amount of soft tissue resection required, muscle strength decreased about three grades at the shoulder and two grades at the elbow. The range of motion was significantly decreased in the shoulder, ranging from 67% to 80% in the modes of flexion, extension, abduction and internal and external rotation, and a decrease of 30% to 40% of the elbow range of motion. Postoperative pain was surprisingly nonexistent. Patients had a pain rating on the UCLA pain scale of 9 out of 10 for the femur (10 being pain-free) and 9.5 out of 10 for the humerus. Secondary procedures of the humerus and the femur basically dealt with the treatment of wound coverage and infection. The complication rate was between 25% and 40%. Major complications included allograft fracture, deep and superficial infection that loosened fixation and nerve palsy.

The projected survival in the osteosarcoma limb salvage program seems to be linear, with about 50% of patients alive at the three-year follow-up (Figure 3). At an average follow-up of 2½ years, eight of nine patients with osteosarcoma of the humerus survived; of patients with osteosarcoma of the femur, 12 of 20 survived. In 29 patients, there was one local recurrence, which was probably due to inadequate resection of an intraarticular extension of the tumor margin at the time of operation. No evidence of skip lesions was found in any of the resected tumors inspected for abnormalities.

Summary

Wide-block excision of bone tumor is a viable technique but does carry a significant risk of postoperative complications. The use of allograft in combination with chemotherapy and irradiation does not seem to be a successful mode in the treatment of these skeletal defects. Endoprosthetic replacement when combined with chemotherapy seems to provide an alternative to allografting. Other authors have reported good to excellent results in resecting large tumors without the use of chemotherapy, but the local recurrence rate is significantly higher than that experienced with the UCLA protocol.

Preoperative intraarterial administration of doxorubicin and radiation therapy have a dramatic effect on tumor histology and seem to improve the control of local recurrence. The use of metallic endoprosthetic replacement when combined with chemotherapy and irradiation offers a viable choice to allografting, but does have potential and definite failure rates associated with total joint replacement. Function of the extremity involved is significantly limited in strength and motion but is accepted by patients. The overall survival rate does not seem to be jeopardized by en bloc resection, which, when used in conjunction with chemotherapy, appears to control local recurrence of the tumor.

The Application of Electrical Stimulation in Orthopedic Operations

GERALD A. M. FINERMAN, MD:* In 1953 investigators noted that electrical charges could be measured when forces were applied to bone. These charges were termed

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stress-generated potentials and were not dependent on cell viability. Areas of bone under compressive loads had a negative electrical charge, whereas areas under tensile forces had a positive electrical charge. It has been hypothesized that changes in electrical potentials are an important stimulus to bone formation and resorption in response to mechanical stresses as described by Wolff's law. Further investigation identified bioelectric potentials, which are dependent on cell viability. Areas of bone growth are electronegative; inactive areas are either electrically neutral or electropositive. Measurement of electrical charges in single osteons has shown the change in potential to be related to the application of tensile or compressive stresses. The cellular mechanisms by which electricity affects bone are not well understood. However, it has been suggested that electricity affects the cell membranes to increase production of adenosine 3′:5′-cyclic phosphate modulating basic cellular functions.

These observations have led investigators to apply electrical charge to bone in attempts to induce bone formation and thereby heal nonunions. In the first method devised by Brighton and colleagues,[10] they applied a negative charge at the fracture site by placing an electrode percutaneously. An external power source was applied and 20 μA of current provided for a 12-week period. This technique was termed semi-invasive, requiring a slight surgical procedure; it required, however, careful placement of the electrodes and care to avoid infection around the electrodes.

The second technique is that of implanting an entire unit, including the power supply and electrodes, and removing it surgically after the power supply fails. This method permits precise placement of the electrode but requires two surgical procedures and reoperation if the power source fails.

The third clinical method, developed by Bassett and co-workers,[11] induces a current in bone by placing a Helmholtz coil, which generates a pulsating electromagnetic field, about the fracture site. The pulsating electromagnetic field induces an electrical field at the nonunion site. Although this method is noninvasive, it requires a bulky nonportable device that must be connected to fixed power sources.

A fourth method being developed by Brighton and associates makes use of capacitive coupling to induce an electrical charge in bone. This technique, being noninvasive and portable and thereby assuring patient compliance, is under clinical investigation.

Brighton and colleagues[10] have reported their results using the semi-invasive application of a direct 20-μA current in the treatment of 258 patients with nonunion at varying sites. In their multicenter study, 80% of patients with nonunions had healing. Bassett and coworkers[11] have also reported their results using noninvasive pulsating electromagnetic fields in 125 patients with nonunion of the tibia. In their study, 87% of patients had healing of their nonunions. Both investigators found that synovial pseudarthrosis failed to heal. Resection of the jointlike surfaces was necessary for healing to occur. This type of nonunion can be identified by a cleft between the bone fragments on bone scan with bone-seeking radionuclides.

Figure 4.—X-ray examination 19 months postfracture shows nonunion of tibia, with hypertrophic callous formation and varus deformity.

Report of a Case

I will present a case history to illustrate the use of electrical stimulation for the treatment of nonunions. The patient, a 25-year-old draftsman, was initially injured in 1977 when his motorcycle was struck by an automobile. He sustained a fracture of his femoral neck and midshaft femur and a compound fracture of the tibia and fibula. The tibial fracture was debrided and the patient placed in traction. Two weeks later the patient underwent open reduction of his femoral fractures and the insertion of Kirschner wires into the tibia with cast immobilization. The femoral fractures healed; the tibia, however, did not.

At his first UCLA visit 19 months postfracture, the tibial skin wounds had healed and the tibia had shortened by 2 cm. There was motion at the tibial fracture site and the patient had a 10-degree varus deformity. X-ray examination (Figure 4) showed nonunion with hypertrophic callus and varus deformity.

At 21 months postfracture, the patient underwent a

surgical procedure to have a Wagner external immobilization apparatus inserted for correction of his deformity, to osteotomize the fibula and to have electrodes inserted for semi-invasive direct-current stimulation. X-ray films showed the Wagner apparatus and electrodes in place with correction of the varus deformity (Figure 5). Electrical stimulation was maintained for three months along with immobilization in the Wagner apparatus. The patient was placed into a patella-tendon-bearing cast for an additional three months until fracture healing could be definitely determined radiographically. An x-ray examination at about two years after electrical stimulation showed fracture union, early tibial remodeling and correction of deformity (Figure 6).

The clinical use of an electrical charge to accelerate bone formation is in its early development phase. Investigation of the basic processes by which electrical charges modulate cellular activity in bone is necessary before we realize its full potential. The application of electrical charges may be helpful in fracture healing, prosthetic fixation and treating bone resorption, osteonecrosis, osteomyelitis, limb length inequality and metabolic bone disease, such as osteitis deformans.

Vascularized Bone Transfer

ROY A. MEALS, MD:* Microvascular surgical techniques developed recently have made it possible to replant amputated limb parts and to transfer living tissue from one area of the body to another. Vascularized bone transfers are one such example.

Reconstruction of large bone defects has traditionally proved to be difficult for several reasons. The osteogenic cells in a conventional (devascularized) bone graft survive solely by diffusion until new capillary ingrowth occurs. This means that at best only a few cells survive within the rigid crystalline structure of the bone and that the graft is slowly incorporated into the spanned defect by a process known as "creeping substitution." This term accurately acknowledges that a standard bone graft provides only a calcium framework on which cells migrating from adjacent tissues proliferate and revitalize the bone. The process of "creeping substitution" takes many months or years. Until it is complete and the bone has been entirely revitalized, the graft is structurally unsound and prone to infection.

Using microsurgical techniques, it is feasible in many

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Figure 5.—Photograph of x-ray showing Wagner apparatus and electrodes in place.

Figure 6.—X-ray examination shows fracture union and early tibial remodeling, about two years after electrical stimulation.

cases to circumvent the problems of traditional bone grafting when reconstructing large segmental skeletal defects. Donor bone can be harvested from one of several favored sites where the nutrient vessels can be isolated with the bone segment. When the bone is transferred to its recipient site, the nutrient vessels can be anastomosed to local vessels and thereby provide immediate blood flow to the transferred bone. The transferred cells survive fully because their blood supply is only temporarily interrupted, and the bone, therefore, maintains its resistance to infection and mechanical stress. The body "sees" the reconstruction as only several "fractures" in living bone; the skeleton is restored as soon as fracture healing occurs between the transfer and the bone ends of the recipient. Thus the reconstruction process is shortened by many months.

Three donor sites are used for vascularized free bone transfers. The posterior rib along with its intercostal artery and associated veins provides a somewhat short and curved bone segment, but has proved to be useful for mandible reconstruction. A segment of fibula, up to 40 cm in length, is the most versatile strut type of free bone transfer using the vasculature supplied from the peroneal artery and associated veins. A segment of iliac crest, transferred with its internal circumflex iliac artery and associated veins, can provide a plate of bone of varying dimensions. Each of these donor sites can be closed with very little functional or cosmetic morbidity to a patient.

In the recipient bed the transferred vessels are anastomosed to available local recipient vessels. Because the transferred bone brings most of its own blood supply, this bone can survive in irradiated or mechanically scarred beds. Diffusion of nutrients from surrounding healthy tissue is unimportant compared with the demands of a conventional bone graft.

Because the technique requires meticulous dissection of the donor bone to avoid injury to its vascular supply, and because it requires careful connection of the vessels that may be as small as 0.5 mm in diameter, the surgical procedure takes many hours and is not the panacea for skeletal reconstruction. General indications include segmental long-bone loss of 6 cm or more, and shorter seg-

Figure 7.—Photograph of an x-ray showing a congenital pseudarthrosis of the right tibia in a 2½-year-old child that has not healed after multiple bone grafting and electrical stimulation procedures.

Figure 8.—By six months after operation the vascularized fibula transfer from the left leg (of the patient in Figure 7) has solidly healed at both ends **(arrows).**

mental bone loss that has been resistant to less complicated reconstruction efforts. Conditions for which free vascularized bone transfers have been successfully used include reconstruction for congenital tibial pseudarthrosis and traumatic nonunion of the tibia, femur or humerus, with or without infection.[12] Vascularized bone transfers are also used for long-bone reconstruction after segmental excision of benign but aggressive tumors, as well as low-grade malignant tumors such as giant cell tumor, adamantinoma and chondrosarcoma.[13]

A representative case is a 2½-year-old child who had congenital pseudarthrosis of the tibia that had failed to heal after conventional bone grafting and electrical stimulation techniques were applied (Figure 7). The traditional resolution of similar cases of resistant pseudarthrosis has been to amputate below the knee and to fit with a prosthesis. Preoperative arteriograms confirmed a normal vascular supply in both the donor and recipient legs. A 6-cm segment of fibula from the uninvolved lower limb was removed with the peroneal vessels and the nutrient vessels branching into the bone segment. This bone segment was transferred to the pseudarthrosis site in the involved leg, and the donor peroneal vessels were anastomosed to the recipient anterior tibial artery and associated vein. The limb was internally stabilized with a plate and screws. The procedure took eight hours. Bone scans done on the fourth postoperative day showed rapid isotope uptake in the transferred bone, indicating that its blood supply was intact. By six months after the operation, the graft had united to the tibia at both ends and was beginning to hypertrophy to meet the child's weight-bearing demands (Figure 8).

Figure 9.—A Charnley total hip replacement in a 60-year-old woman with osteoarthritis.

Advances in Joint Replacement Fixed With Acrylic Cement

Total Hip Replacement

JOHN R. MORELAND, MD:* In 1962 Sir John Charnley of England developed modern total hip arthroplasty.[14,15] He replaced the femoral head and neck with a small metallic head and neck attached to a metallic stem, which was then fixed in the femoral intramedullary canal with methyl methacrylate cement (Figure 9). The surface of the acetabulum was replaced with a thick piece of high-density polyethylene, also fixed to the bone with methyl methacrylate. This design concept represented a quantum leap in the surgical ability to give a patient with arthritis of the hip consistent pain relief with excellent range of motion; this procedure has remained basically unchanged during the 20 years since. Charnley called his operation "low friction arthroplasty of the hip." The coefficient of friction between the highly polished metal ball and the polyethylene acetabular component is low. The frictional torque applied to the acetabular component is directly proportional to this coefficient of friction and to the metal ball radius. This frictional torque can cause failure of the methyl methacrylate fixation. Small head sizes are thus used to minimize the frictional torque transmitted to the acetabular component.[14,15]

An estimated 75,000 total hip replacements are done yearly in the United States. Significant relief of pain without serious complications occurs in more than 90% of cases. This success rate has been higher than with either cup arthroplasty or femoral osteotomy. Teflon initially used in acetabular component material of total hip replacements had a high wear rate and it was feared that wear would also be a problem with polyethylene. High-density polyethylene currently used for the acetabular component has an extremely low wear rate along with its low frictional property. Wear has not been a clinical problem with polyethylene.[16]

Fatigue fracture of the metallic stem has occurred at a low rate but with higher strength alloys a larger margin of safety has now been provided. Infection occurs in about 1% of previously unoperated hips and is a serious complication because it usually requires removal of the prosthetic components before the infection can be controlled. Dislocation of the compo-

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nents, which is more likely in the perioperative period, can usually be treated by closed reduction and then careful positioning until the hip forms mature scar in the periprosthetic space. Repeated dislocations usually indicate inappropriate positioning of the components and may require surgical revision. Some patients, particularly men with osteoarthritis, have the complication of heterotopic bone forming in the periprosthetic space. This bone formation results in restriction of hip range of motion but only occasionally causes pain. This bone can be resected later and its reformation inhibited by diphosphonates and irradiation. Nerve palsies have occasionally occurred postoperatively but most resolve.[17]

The major long-term complication of hip replacement operation is loosening of the implants. The prostheses are fixed to the bone with methyl methacrylate cement, which acts not as a glue but as a grout. The fixation is achieved by multiple small mechanical interdigitations of the cement into trabecular irregularities. With time and stress, this initially achieved fixation can fail, with resultant loosening of the components. The movement of the prosthesis-cement composite against the bone may eventually cause pain and sometimes incites a histiocytic and macrophagic response so that bone resorption also occurs over and above what would be expected from mechanical abrading away of bone by the loosened prosthesis. The individual tendency for bone resorption with loosening varies. This loss of bone stock makes surgical revision more difficult because of the lack of firm bone on which to recement a new prosthesis.[18,19]

Figure 10.—A surface hip replacement in a 52-year-old woman with osteoarthritis.

The revisional rate in a series of 444 replacements followed for a mean of four years at UCLA was 1.1% for the acetabulum and 2.7% for the femoral component.[19] Charnley reported in a series with 12- to 15-year follow-ups 0.9% acetabular and femoral revision rates.[16] Most other large centers report similarly low revision rates. Several researchers have scrutinized follow-up x-ray films for signs of loosening and have radiologically found a high incidence of loosening. Most hips that show signs of loosening by x-ray study are not symptomatic enough to necessitate surgical revision. Factors contributing to loosening are the duration of follow-up, the degree of stress placed on the implant and the quality of the initial surgical procedure.

Because aseptic loosening is the main cause of failure of hip replacements, efforts have been made to improve the technique of cementation. By obtaining better cement interdigitation into the bony trabeculae, a more durable fixation results. Pulsating lavage and brushes have been used to clean the bone before cementation. Bleeding has been minimized through the use of hypotensive anesthesia and careful attention to hemostasis. To increase cement interdigitation, pressurized cement in a low viscosity state is now used. Handling low viscosity cement requires the use of cement guns, which are also useful for cement pressurization. The femoral canal is now plugged to prevent migration of cement down the canal and also so that the cement can be pressurized before prosthesis insertion. These modern techniques should result in more durable hip replacements.[20]

Surgical revision is becoming more and more common. The durability of a revision hip replacement is not as good as that of a hip replacement being done for the first time because of the increased complexity. Bone stock loss can eventually preclude reconstruction and thus a patient is left with a hip joint supported by soft tissue scar. This type of hip is referred to as a Girdlestone arthroplasty or a resection arthroplasty and is characterized by a short extremity that is unstable but only minimally painful. The patient usually needs one or two walking aids for ambulation.

During the late 1970s, both here and abroad, several researchers developed a new type of hip replacement called surface replacement arthroplasty.[21] In this type of hip replacement, the head and neck are not resected; rather, the head is simply covered with a metal shell cemented in place (Figure 10). The acetabulum is then resurfaced with a thin polyethylene shell. This type of arthroplasty preserves femoral bone stock, making revision of the femoral component easier. It was hoped that this arthroplasty would be more durable than conventional hip replacement. Multiple centers have reported high failure rates with this prosthesis due to femoral and acetabular loosening as well as femoral

neck fractures, but this has been primarily due to its use in youthful and hence more active patients and those with deficient bone stock. The technique is also demanding and at present its use is confined to a few centers.[21] The best indications are in middle-aged patients with osteoarthritis or other patients with arthritis and good bone stock.

Total Knee Replacement

Total knee replacements followed quickly in the United States after hip replacement was introduced around 1970.[22] The initial hip replacement results were so promising that many researchers were inspired to design and to test different knee prostheses. These first knee replacements were not as durable or as reliable as hip replacement because of frequent tibial loosening, patellofemoral pain (because it was usually not replaced), poor range of motion and instability. Hinge knee replacement was particularly unsatisfactory: a high incidence of loosening occurred due to high forces transmitted to the cement bone interface because of the linkage. Infection was also higher with the hinge prostheses.

In the late 1970s condylar type knee replacements were developed.[23] With these designs, all of the articular cartilage surfaces of the femur, patella and the proximal tibia were basically resurfaced with surfaces more similar to the contours of an anatomical knee than the earlier devices (Figures 11, 12). Thus, in most modern knee replacements the patella is resurfaced with a cemented piece of polyethylene (Figure 13). The patellar component articulates with the metal of the femoral component during knee range of motion. The knee components are fixed to the bone with methyl methacrylate cement in a similar manner to that of hip replacements. Many knee replacement surgeons feel that modern knee replacement is as successful as hip replacement.

Tibial component loosening was one of the major early problems of knee replacement procedures. This problem has been minimized by using tibial components that have a short central peg and cover the entire proximal cut surface of the tibia, thereby resulting in a stronger composite structure. As knees become arthritic, many deformities of genu varum or genu valgum develop. If prosthetic knees are left with this deformity, an overload results in the compartment of the knee that is on the concavity of the deformity. If correction of the knee deformity is done at the time of operation, a more durable prosthetic reconstruction is obtained. Restoration of alignment is now one of the major goals of knee replacement, using techniques of ligament release but preserving stability.

Other Major Joint Replacements

Shoulders have been replaced with similar types of materials using a polyethylene component and a metal humeral component (Figure 14). Various designs are available. Pain relief has been achieved but results are

Figure 11.—Bilateral total knee replacement in a 67-year-old man with rheumatoid arthritis.

Figure 12.—A lateral view of a total knee replacement.

not as satisfactory when there is a deficient rotator cuff or bone stock loss after trauma. The best results have been in cases of osteoarthritis and osteonecrosis. Patients who have cuff deficiency are placed in a "limited goals" category of providing pain relief.[24]

The many replacement versions developed for ankles have had a high incidence of aseptic loosening, instability and poor range of motion. When aseptic loosening occurs in an ankle replacement, surgical revision is difficult; fusion is also difficult because of a loss of bone stock. An alternative operation, ankle fusion, gives a good functional result. These considerations have limited the indications for ankle replacement to patients with rheumatoid arthritis.

The elbow has also been replaced with metal and polyethylene devices fixed with acrylic. Several different prostheses are available. The major problems with elbow replacement procedures have been instability and loosening. Indications for this operation are infrequent and again primarily restricted to patients who have rheumatoid arthritis.

New Method of Fixation—Porous Ingrowth

WILLIAM C. KIM, MD:* The most common and perplexing complication of cemented total joint replacement is delayed loosening at the bone-cement interface. Loosening is a serious problem because it leads to progressively increasing pain, abnormal joint function and joint-supporting bone loss. Revision of a total joint replacement may be required, heralding repetitive and accelerated cycles of loosening and revisions of diminishing durability. Loosening is a major unsolved problem in cemented total joint replacement.

The pathogenesis of loosening may be conceptualized as time-related loss of mechanical interlock between bone and cement achieved at operation. Fixation failure occurs when stress (force per unit area) exceeds strength of bone-cement interface. The stress for failure may be a single large impact load but is usually the result of a cumulative effect of smaller loads exceeding the fatigue properties of both the bone-cement composite and biologic reparative ability. The failure threshold is modulated through biologic response to transmitted interfacial stress and biocompatibility properties conferred by material, structure and spatial relation of bone and the cemented implant. Stress characteristics outside the physiologic range exaggerate normal bony remodeling according to Wolff's law.[25] Bone hypertrophies at interface points where transmitted stress is excessively high (stress concentration); bone resorption occurs where stress is abnormally low (stress shielding) (Figure 15). Cement is the biomechanically weak link in the bone-cement-implant composite. Its deformation characteristic is mismatched with bone and implant; uneven stress transmission is amplified by uneven cement layers and unstable bone-cement interdigitation, predisposing to loosening.

Under the best of mechanical circumstances, cement tends to activate a thin interfacial fibrous membrane response, indicating a degree of bioincompatibility. This is true even in strong and stable bone-cement interface, which will endure if it is stable.[26] Interfacial motion enhances this response; its thickness and organization parallel the magnitude and direction of motion. With significant loosening, abrasive metal, polyethylene and cement particles incite foreign body histiocytic and giant cell reactions, which in turn seem to mediate interfacial osteoclastic bone resorption (personal observation).

The biomechanical factors pertinent in loosening may be minimized by careful patient selection, assessment of the underlying joint disease and improved implants and surgical techniques. In time, however, an increasing number of cemented total joint replacements is predicted to loosen. That bone-cement fixation system has finite durability, especially in young active patients, is evidenced by a 57% failure rate at five years in patients younger than age 30 years.[27] A more durable

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Figure 13.—A sunrise view of total knee replacements.

fixation system is needed, especially in the youthful population, because no major improvement in the bone-cement system is likely.

In the early 1970s an alternate system for fixing bone and implant seemed promising: bone-implant fixation by bone growing into porous-surfaced implants.[28-30] Although it was theoretically more physiologic and supported by laboratory data, the phenomenal early benefit brought to many patients by the cemented total hip replacements probably delayed refinement and clinical application of the porous-ingrowth fixation system. A significant incidence of late bone-cement loosening has now encouraged its serious consideration as an alternative.

Figure 14.—A total shoulder replacement in a 70-year-old woman with osteoarthritis.

The evolution of porous-ingrowth systems to the present clinically applicable state was one of understanding biologic and mechanical requirements for strong and durable porous fixation. The area of elucidation required technologic advances in implant material, design and fabrication consistent with biomechanical principles governing interfacial stress and biologic response.

The phenomenon of bone ingrowth is incompletely understood but the mechanism is an expression of healing and maturation and a remodeling response to a porous-surfaced implant. The initial event is osteoconduction, the intrinsic drive of bone to grow into a juxtaposed porous network of suitable material and configuration. The ingrown bone then undergoes maturation and remodeling, sustained and directed by interfacial stress transmission characteristics. Osteoconduction has four established requirements: viable bone, biocom-

Figure 15.—Stemmed femoral component: Stress preferentially follows paths of greatest stiffness. At sites of stress concentration bone hypertrophies; at sites of stress shielding, bone resorption occurs.

patible material, a range of optimal pore size and intimate and stable apposition of bone-porous interface.

Bone ingrowth by definition requires viable bone. Local and systemic factors governing the healing response are pertinent. Significant avascular necrosis of juxta-articular bone seems to be a contraindication for this fixation system.

Second, the porous-surfaced material must not possess ingrowth inhibitory properties, that is, it must be biocompatible. Various materials fulfill this criterion: polymer,[31] ceramics,[32] ceramic-epoxy composites[33] and certain metals.[28-30] Suitability of these materials for clinical application is restricted by their strength, compliance, fatigue and corrosion and fabrication properties. Polymers are generally weak and lack durability, with low modulus; under dynamic loading, interfacial micromotion occurs, which is a deterrent to bone ingrowth. Fabrication characteristics of ceramic permit uniform porosity of desired size but it is brittle and fails by crack propagation.[34] Ceramic-epoxy composite (Cerosium) possesses improved deformation characteristics but degrades in vivo.[34] Of materials presently available, cobalt-chromium and titanium alloys show promise.

Alloys of Co-Cr in various forms have been used in humans for several years without discernible deleterious effects. A porous texture is achieved by sintering powder of Co-Cr beads onto the core implant. Histologic studies of bone-porous interface show minimal to no fibrous response.[35] Cobalt-chromium-molybdenum implants in soft tissue of rats did not show neoplastic induction at two years.[36] Wapner and associates[37] recently reported that chromium (VI) may suppress immune defenses in rats. Immunologic response and cross-reaction between cobalt and nickel have been seen in rabbits.[38] Increased local and systemic ion concentration has been noted but its significance is unknown. Although Co-Cr is strong and resistant to fatigue, the composite beaded layer is relatively brittle and may fail by crack propagation.[30]

Titanium, a relatively new metal in clinical use, seems to have certain advantages.[30,39] The configuration is a fibermesh of desired pore dimensions and density, achieved by sintering compacted titanium fibers to the implant. Its deformation property can be matched to trabecular bone and it does not fail by crack propagation. This theoretically results in more even stress distribution at bone-porous interface without associated pathologic bone remodeling. Titanium is well tolerated by host tissue and it appears to be accepted as part of the host tissue.[40] Increased local and systems ion concentration has been reported but its significance is unknown.[41] Surface area is increased 18-fold in this porous system.[39] At six weeks, titanium fibermesh-bone achieves the strength of cement-bone at operation.[39]

The third requirement for bone ingrowth is that the pore opening dimension be within a specific optimal range. Although data vary depending on material, laboratory animal model and static versus dynamic loading, this range seems to be 50 to 500 microns. Below 50 microns only fibrous ingrowth occurs[42]; above 500 microns (macropore size) fixation strength is achieved by contouring bone at irregular surface and not by bone ingrowth. The optimal range seems to be 50 to 250 microns, consistent with unit trabecular and osteonal dimension. In a ceramic-canine model, a pore size greater than 75 microns supported the haversian system.[43] If there is micromotion, the critical mean pore diameter for ingrowth is larger[44]; stability of the interface and the deformation property of porous material are variables.

The fourth requirement is that the bone-porous interface be intimate and stable (rèlatively free of motion). Motion results in fibrous ingrowth. If the interface is stable, small gaps (to 1.5 mm) may be bridged by bone.[35] The long-term stability of the interface is dependent on bone ingrowth but it takes three to six weeks to achieve substantial strength equal to immediate strength conferred by the cement system.[39] Immediate intraoperative stability is mandatory, achieved by a precision-interference fit of implant to bone.

An osteoconduction front progresses inward linearly with time. Given sufficient time, the thickness of the porous layer and provided osteoconductive conditions are met, ingrowth continues. This osteoconduction front undergoes maturation and remodeling, which are dependent on time, type of substrate bone (cortical or cancellous) and design (configurations of porous surface and core implant) and stress characteristics at the bone-pore interface. Mechanical properties of the porous-ingrowth composite parallel the extent and degree of maturation and remodeling.

That maturation and remodeling are time-dependent has been observed and is consistent with remodeling after bone injury. There are centripetal ingrowth and maturity gradient.[32] Cortical bone ingrowth, maturation and remodeling take longer than implant interfacing with cancellous bone, and are explained by the slower turnover of cortical bone.[45] Stress follows the paths of greatest stiffness. Inadequate implant material and design, which concentrate and shield stress, are expected to direct pathologic remodeling.[46,47]

The shear strength of bone-porous interface depends on the extent of bone-porous interface,[48] depth of ingrowth and maturation state of ingrown bone.[32] The weak link in this system is bone-porous interface. Shear tests regularly result in failure at this junction.[32] Shear strength of porous-trabecular bone composite is weaker than the porous-cortical system,[45] but trabecular bone strength can be increased with hypertrophy and cortical bone can be weakened with resorption. The ultimate interfacial shear strength does not exceed that of underlying bone.

Interface strength can be controlled by altering the material configuration. Shear strength is increased by increasing the number of porous layers.[49] This is attributed to three-dimensional bony interlock; it also confers increased strength in torsion[50] and tension.[49] A

porous system is distinctly superior to a cement system in these important modes of loading. In a pull-out test of porous-surfaced plates, there was little difference in shear strength for a pore size range of 50 to 400 microns.[49] Shear strength increases with time as a result of maturation of interlocking bone and increasing surface contact area and volume of ingrown bone.[32] Shear strength plateaus at six weeks[30,32] in dogs, which suggests a diminishing contribution of deeper ingrown bone to strength. Fibrous ingrowth yields significantly less strength than ingrowth bone. A porous implant in cortical bone possesses greater shear properties than the same implant in cancellous bone.[48]

The key consideration in the clinical application of porous systems is its durability under long-term dynamic loading. Titanium fibermesh on stemmed total hips implanted in dogs showed durable bony fixation (up to one year); ingrowth was regional around the stem,[39] probably reflecting regional variation in stress characteristics. Our understanding of the determinants of long-term dynamic stress-ingrowth is incomplete and is of critical importance in modeling optimal porous joints. Elucidation of the underlying biomechanical laws is under active investigation at UCLA Medical Center and other centers.

A previous study at UCLA Medical Center involved cemented-surface (stemless) total hip replacements in dogs. Delayed complications included loosening, neck fractures, pathologic bony remodeling and a variable fibrous membrane response at the bone-cement interface (Figure 16). Surface replacement arthroplasties in patients have been successful and are comparable with

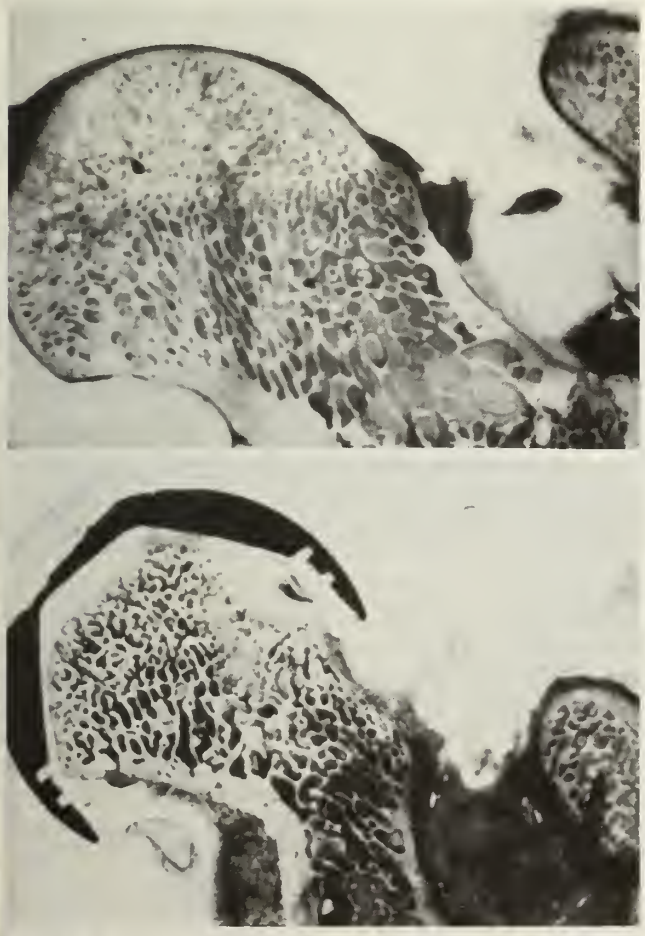

Figure 16.—Comparison of normal and cemented femoral surface replacement. **Top,** Ground section of normal canine femoral head. **Bottom,** Ground section of cemented surface replacement six months postoperatively. Note neck thinning and interposed fibrous membrane between cement and trabecular bone.

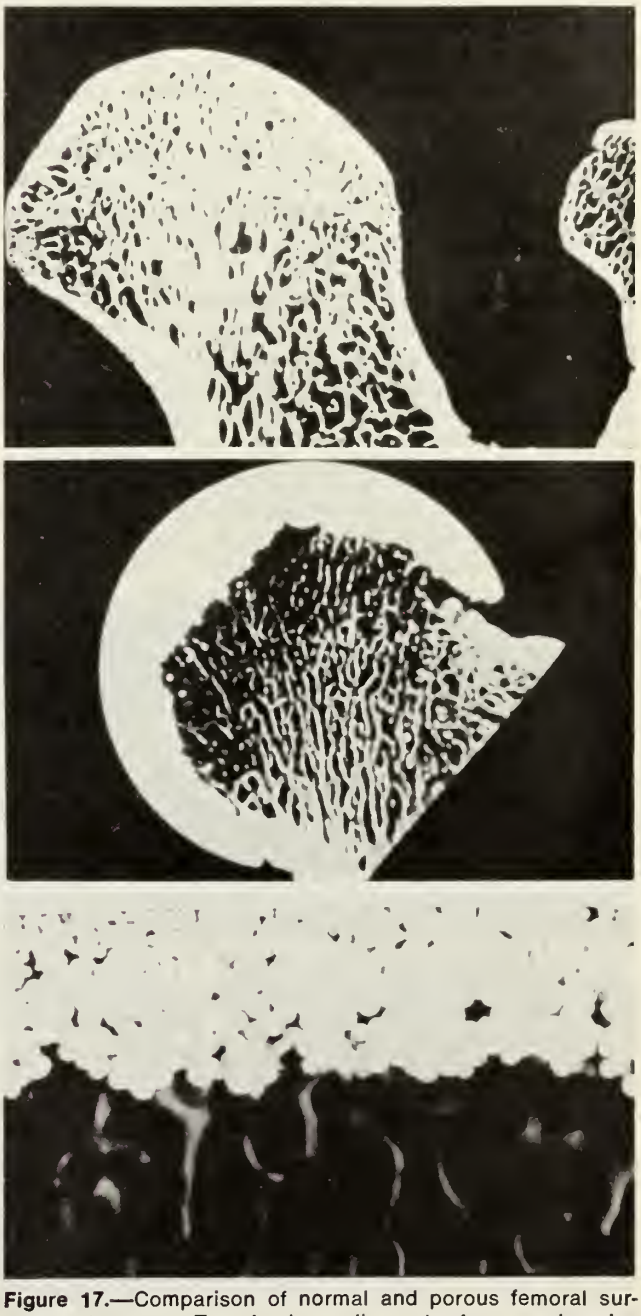

Figure 17.—Comparison of normal and porous femoral surface replacement. **Top,** A microradiograph of a normal canine femoral head. **Center,** A microradiograph of a porous femoral surface replacement two years postoperatively. Note the maintenance of normal trabecular density and pattern, indicating long-term biomechanical compatibility. **Bottom,** A magnified view of bony ingrowth into porous femoral cup. (Each pore diameter is approximately 200 microns.)

stemmed total hip replacements at UCLA. The complications have been similar to those in dogs, with an uneven stress transmission and membrane response.

A similar evaluation of long-term replacement in dogs has also been done.[47] The porous materials studied include sintered Co-Cr beads and titanium fibermesh. After implantation in hips, dogs were permitted free activity and were noted to be fully weight-bearing at the third week. Radiographs of hips were taken at regular intervals. The sacrifice schedule permitted time-dependent (up to two years) microradiographic and ground-section analyses of the bone-porous interface at the femoral head and acetabulum. Long-term specimens showed extensive and deep bony ingrowth; regional stress trabecular patterns were remarkably similar to those of contralateral unoperated hips (Figure 17). A microscopically intimate contact between trabecular bone and porous metal was observed (confirming a previous study)[30] and fibrous membranes were infrequent and minimal. Bony ingrowth and fibrous membrane may be a function of stress distribution. (In general, stress transmission in a porous system is presumed to be smooth and physiologic.) Factors influencing a stress pattern without pathologic bone remodeling are being analyzed, including the role of the surgical technique, prosthetic position and orientation and interfacial remodeling behavior to this implant design. Complications occurred early in the project and included dislocations, loosening and neck fractures directly attributable to poor surgical technique. The basic concept of porous ingrowth is supported. The short-term results in human porous total hip and total knee replacements at UCLA and other centers are encouraging.

Unknown areas of future concerns include long-term clinical durability, biocompatibility, metal corrosion, wear, infection and removal. Facilitating ingrowth by electrical stimulation and certain materials is interesting but the clinical role is uncertain.[51,52] Infection has been infrequent but disastrous in cemented total joint replacements, whereas there is evidence in dogs to suggest that resistance to infection may be increased when cement is not used.[53] Wear is predicted to be a real problem but less of one than in cemented total joints. Corrosion has been discussed because of the increased surface area. Removal of a porous implant encased in bone will be difficult; its solution lies in developing special instruments to minimize bone removal. Data now strongly support the soundness of a porous ingrowth concept and a hoped-for long-term durability.

Bone Morphogenetic Protein and Bone-Derived Growth Factors

MARSHALL R. URIST, MD:* In 1980 a UCLA Interdepartmental Conference on Growth Factors was organized by David W. Golde, MD.[44] Growth factors are growth-stimulating substances that are not nutrients. Metabolic substrates, cofactors, vitamins, amino acids and minerals are classified as nutrients rather than growth stimulants. Growth factors (also referred to as local hormones) are synthesized by a wide variety of tissues for stimulating DNA synthesis by the same or different cell type. At the 1980 conference, 12 different factors were known. More than ten additional growth factors have been reported since then, and the list is steadily growing. Included in this list are bone morphogenetic protein and bone-derived growth factor. Bone morphogenetic protein (BMP) is a component of bone tissue and its function is to induce differentiation of perivascular mesenchymal-type cells (pericytes) into osteoprogenitor cells, cartilage and bone.[55-60] Osteoprogenitor cells secrete bone-derived growth factor that stimulates DNA synthesis.[61-66] BMP and bone-derived growth factor are parts of the paracrine, a local-acting system as distinguished from the endocrine (long-distance-acting) system. The action of BMP and bone-derived growth factor is coefficient. BMP irreversibly induces a mesenchymal cell population to disaggregate, migrate, reaggregate and differentiate, whereas bone-derived growth factor reversibly stimulates osteoprogenitor cell proliferation and growth.

According to modern concepts of development, morphogenesis precedes cell differentiation and proliferation.[67] The morphogenetic phase of development is characterized by cell disaggregation, migration and reaggregation. The cytodifferentiation phase is characterized by growth of a specialized tissue or organ. Although BMP influences the genome, the detailed molecular mechanisms are not known. Bone-derived growth factor influences osteoprogenitor cells; the effects are comparable with those of other growth factors or somatomedin in nature. The aim of contemporary research is to characterize completely BMP and bone-derived growth factor and to make these two newly isolated agents available for research on bone cell differentiation and unsolved orthopedic problems.

The extraordinary regenerative capacity of bone has been selected for throughout the vertebrate evolution. Bone is continuously renewed throughout life, irrespective of demand, and regenerates completely and without scar. Other tissues regenerate partially and only from preexisting predifferentiated cells (for example, liver and mucosal cells). Central nervous system cells do not regenerate to any appreciable extent. Whether the unique capacity of bone to regenerate is attributable to BMP-induced differentiation of pericytes, to proliferation of preexisting bone cell precursors or to a combination of induced differentiation and precursor cell proliferation is the central question confronting researchers on fracture healing, bone grafting, osteoporosis and other skeletal system disorders.

The formation of bone by proliferation of osteoprogenitor cells is well known and measured either by reactions of endosteum and periosteum to bone injury or to alterations in dietary minerals and vitamins, or perturbations of the endocrine system, including parathyroid hormones and other hormones. The process of bone formation by BMP-induced cell differentiation is

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less well known, and was not appreciated until bone matrix-induced bone formation was reported in 1965.[68]

Historically, four observations led to the present concept of bone morphogenetic protein. The first was the discovery that allogenic implants of demineralized bone matrix induced bone cell differentiation and formation of an ossicle filled with bone marrow.[69,70] The second was the finding that the BMP component of bone matrix was a chloroform-methanol, neutral salt-insoluble, 0.6N hydrochloride-insoluble, trypsin-labile protein.[55,71,72] The third step was the finding that BMP was a collagenase-resistant molecule, soluble and diffusible in body fluids at 37°C.[57] A fourth leap forward came with the discovery that BMP was soluble in 4 mol per liter of guanidine or 0.5 mol per liter of calcium chloride and 6 mol per liter of urea inorganic-organic solvent mixture, and had the essential properties of a hydrophobic molecule.[73-79]

Human BMP is a polypeptide with a molecular weight of 17,500, associated with two other low-molecular-weight (22,000 and 14,000) proteins, which are chemically extracted from the organic matrix including the cells of compact bone. The sources of bone morphogenetic protein are dentin matrix,[73] rat,[75] rabbit,[57] bovine[73] or human bone matrix[79] or mouse[61] and human[79] osteosarcoma tissues. How much of the BMP is derived from cells, cell membranes or extracellular matrix is not known. Prebone morphogenetic protein, probone morphogenetic protein and BMP may appear sequentially in the foregoing three loci. The BMP is assayed by implantation in a muscle pouch in the hindquarters of mice (Figure 18) or in skull trephine defects (Figure 19) in rats, dogs and monkeys. Implants of 5 mg of BMP induce formation of grossly visible bone deposits within two to three weeks. Qualitatively, human BMP and bovine BMP induce identical responses. Quantitatively, bovine BMP obtained from year-old steers is more active in lower doses than human BMP obtained from 20- to 60-year-old humans. In any case, the yield of new bone is directly proportional to the quantity of the implanted BMP. Bone morphogenetic protein is rapidly absorbed and sequentially replaced first by small round cells, macrophages, ameboid mesenchymal cells, spindle-shaped cells and then by hypertrophied connective tissue cells. By days 14 to 21, a fibrous envelope forms around the reactive connective tissue cells. Inside the envelope, differentiation of chondroid, cartilage and woven bone occurs. The chondroid and cartilage invariably grow in the avascular interior while the new bone develops on the vascularized exterior of the implant. During the interval from days 21 to 28, the woven bone is remodeled to produce a shell of lamellar bone filled with bone marrow.

The quantity of BMP relative to the total tissue weight is only 0.001% of cortical bone. The large bones of bovine and human species are almost unlimited in supply for the production of BMP by relatively inex-

Figure 18.—A, Roentgenograms of the thighs of a mouse 21 days after implantation of 10 mg of human albumin **(left)** and 10 mg of human bone morphogenetic protein **(right).** Note the mass of new bone filling the anterior muscles of the right thigh. **B,** Photomicrograph of an implant of human bone morphogenetic protein in the mouse thigh 10 days after implantation of human bone morphogenetic protein **(arrow). C** = cartilage and chondro-osteoid, and **N** = new bone. **C,** Photomicrograph of an ossicle 15 days after implantation of bone morphogenetic protein showing replacement of bone morphogenetic protein with chondro-osteoid **(C)** and new bone **(N). F** = fibrous envelope and **S** = muscle. **D,** Photomicrograph of ossicle 21 days after implantation of bone morphogenetic protein. **R** = marrow cavity, **N** = cortex of new bone and **S** = muscle.

pensive conventional chemical methods.[79] BMP, derived from all presently known sources, is more completely extractable by guanidine hydrochloride (GuHCl) or calcium chloride ($CaCl_2$) urea inorganic-organic mixture than other solvents. The BMP is separated from high-molecular-weight proteins including gelatin peptides under dissociative conditions in 4 mol per liter of guanidine hydrochloride, and recovered with several other low-molecular-weight proteins by differential precipitation under associative conditions in 0.25 to 0.5 mol per liter of GuHCl. The proteins are then resolubilized, fractionated by gel filtration, preparative gel filtration or preparative gel electrophoresis and hydroxyapatite affinity chromatography, weighed and analyzed by SDS PAGE.

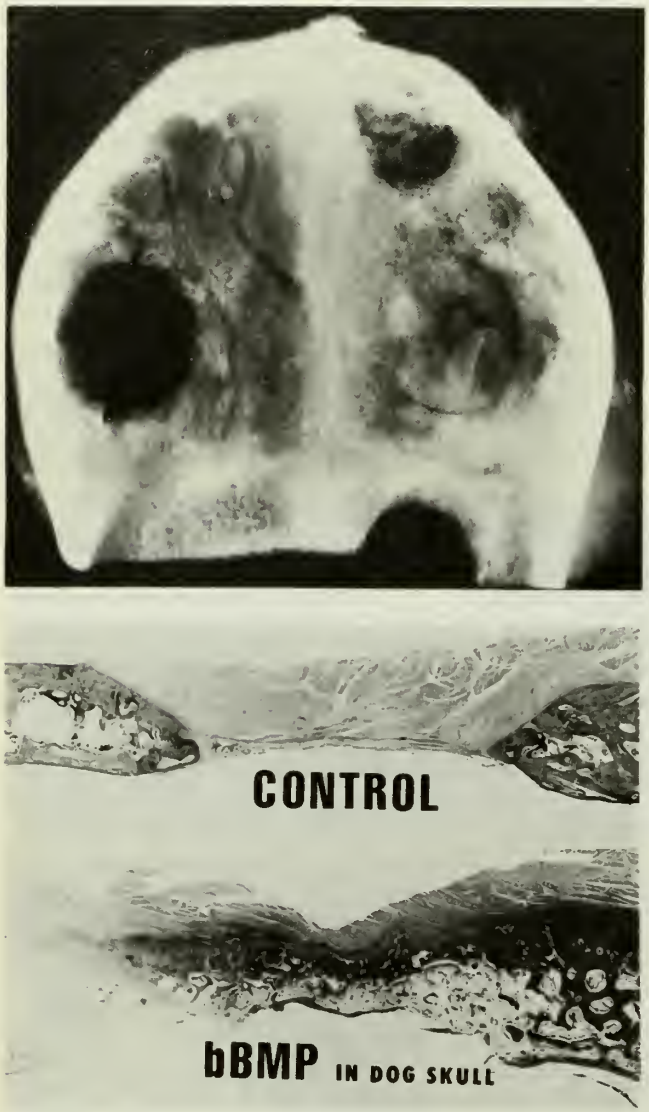

Figure 19.—A, Roentgenogram showing 2-cm skull trephine defects in an adult dog. The control defect on the left was implanted with 100 mg of albumin; the experimental defect on the right was implanted with 100 mg of bovine bone morphogenetic protein. Twelve weeks after the operation, the defect on the left is unhealed, while the one on the right is completely replaced with new bone. **B,** Photomicrograph of the trephine defects in the dog skull in Figure 19A, showing a membrane of fibrous tissue in the control and reconstitution of the skull with new bone and bone marrow in the bovine bone morphogenetic protein **(bBMP)**-treated defect.

Crude protein fractions with BMP activity include proteins with relative molecular masses of 14,000, 17,000, 22,000 and 34,000. All except the 17,500 protein can be removed without loss of BMP activity. The isolated 17,500 component is more rapidly absorbed and induces a lower yield of bone than the crude fractions. Differential analysis suggests that the 17,500 putative BMP, consisting of 20.8% acidic amino acids, is an acidic polypeptide. Monoclonal antibodies to this 17,500 protein have been produced in mice. A radioimmunoassay of BMP is being developed. The *N*-terminus amino acid sequence of each of the low-molecular-weight proteins associated with BMP is under investigation. The possibilities for BMP production by DNA recombinant technology are considerable.

Interesting prospects for the future are for bone morphogenetic protein as a tool for fundamental research on cell differentiation and for investigation of more than 100 bone diseases of unknown causes. That BMP could be the probe for an area as significant as cell differentiation is not unexpected when it is recognized that bone is the hallmark of vertebrate species, developing from mesoectoderm early in embryonic life and regenerating completely and flawlessly throughout all of postfetal life.

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Medical Staff Conference

Regulation of Hematopoiesis

14th Annual Paul Aggeler Memorial Lecture
Given October 18, 1983
San Francisco General Hospital Medical Center

JANE F. DESFORGES, MD, *Boston*

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SANDE:* *Dr Desforges is one of those unusual leaders in hematology who is equally at home with erythrocytes, leukocytes and coagulation problems. She is Professor of Medicine at Tufts University School of Medicine, an associate editor of the* New England Journal of Medicine *and a productive scientist with about 100 publications in hematology. She has been voted outstanding teacher by medical students for eight years at Tufts and is the President of the American Society of Hematology. Dr Desforges showed her considerable clinical skills at our medical staff conference earlier and will now address us on the topic of "Regulation of Hematopoiesis."*

DR DESFORGES:† Hematologic disease is often expressed in a quantitative variation in elements of the circulating blood. The balance between production and destruction can be disturbed on either side. In the past, much attention has been given to physiologic and pathologic mechanisms controlling the rate of destruction of circulating elements in the blood. In cases of hemolytic anemia, for example, shortened erythrocyte survival may be due to an abnormal environment resulting in biochemical, oxidant or mechanical damage or to an abnormal immune response causing immunologic injury. Delineation of the mechanism in an individual case of hemolysis, therefore, has specific therapeutic implications. More recently, attention has been focused on mechanisms that may control the rate of production of cells by the marrow in normal and dyspoietic states. Abnormalities of production may involve one or more cell lines and may affect associated normal hematopoiesis. Impairment of hematopoiesis may occur on the one hand with aplasia induced by chemical or biologic mechanisms or, on the other, with suppression of normal growth due to infiltration by a malignant population. Such failure of normal hematopoiesis may result from impairment of the progenitor cell itself or from abnormalities of accessory cells that have a regulatory function. Again, defining a basis for impaired production in a given case has an important bearing on treatment.

Regulatory Network of Progenitor Cells

Studies during the past decade have provided some insights into the complex network controlling normal production and have also shown the pathologic effects of accessory cells in controlling stem cell growth in some disease states. Results of studies of in vitro hematopoiesis suggest that cell-cell interaction and feedback mechanisms normally play a role in controlling the production of leukocytes, erythrocytes and platelets to achieve a concentration within a narrow range. Effects of accessory cells and cell products in this hematopoietic process can be shown by in vitro culture of pluripotent stem cells or of the progenitor cells committed to a specific line. These systems provide a model for and allow study of cell proliferation and differentiation. In the semisolid cultures generally used, the number, size and cytologic characteristics of

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ABBREVIATIONS USED IN TEXT

B cells=lymphocytes that are programmed for immunoglobulin production
BFU-E=an early progenitor cell for the erythroid series, the burst-forming unit
CFU-E=a late progenitor cell for the erythroid series, the colony-forming unit
CFU-GM=a progenitor cell that is the colony-forming unit for granulocytes and monocytes
T cells=lymphocytes that are processed by the thymus. Subgroups are distinguished by specific surface antigens and functions

a generation of colonies can be evaluated. Using marrow or peripheral blood mononuclear cells as a source of progenitor cells, the environment provided in the culture determines which type of colony predominates.

Multipotent stems cells and committed stem cells, or progenitor cells, are found in the null fraction of circulating mononuclear cells. They lack recognizable characteristics of monocytes or B or T cells. Cohorts of other mononuclear cells—both monocytes and T cells—may, however, have a profound effect on the proliferation of these progenitor cells by either inhibiting or stimulating their growth.

CFU-GM Proliferation

Role of Monocytes and T Cells

The precursor that is the colony-forming unit for granulocytes and monocytes (CFU-GM) requires colony-stimulating activity to proliferate. Monocytes are a source of this, as are T lymphocytes.[1-5] The interaction between monocytes and T cells in providing this stimulus for progenitor cell growth may be complex.[3,6] Stimulation of T cells by a specific antigen and by a mitogen causes release of colony-stimulating activity from stimulated cells. The effect of mitogen is nonspecific. The effect of antigen in animal systems requires repeated exposure in the presence of interleukin 2, a cell product that stimulates T-cell proliferation to provide helper T cells. These antigen-specific T cells then provoke production of colony-stimulating activity from an Ia-restricted cohort of accessory cells. In this setting, then, the colony-stimulating activity is a side product of an immune response.[7]

The role of T cells in controlling release of the factor depends on the setting. Verma and co-workers have shown modulation of colony-stimulating activity production with varying treatment of the T cells.[6] Untreated T cells produce little colony-stimulating activity. Monocytes and T cells together produce greater amounts of the activity than monocytes alone. Incubating monocytes and T cells with a methanol extract of bacille Calmette Guérin increases colony-stimulating activity production whereas prior exposure of T cells to concanavalin A or thymosin decreases it. Other reports show inhibitory effects of T cells exposed to pokeweed mitogen and then assayed in culture. This effect has been attributed to activating T cells bearing IgG receptors and their possible interaction with other cohorts to suppress CFU-GM.[8,9] Mitogens such as phytohemagglutinin, however, stimulate production and release of colony-stimulating activity from T cells.[10-13] While such responses are in some ways analogous to the action of T-helper or T-suppressor cells in the immune response, there is no evidence that the effects on colony-stimulating activity production are mediated by the same cohorts that affect immune regulation.[14]

Feedback Regulation

A mature end product of the CFU-GM, the neutrophil, contains lactoferrin in its granules, the secretion of which appears to induce feedback inhibiting progenitor cell proliferation.[15] Broxmeyer has shown that this effect is the result of decreased production of colony-stimulating activity and Bagby and associates have suggested that lactoferrin-induced inhibition occurs via an effect on the T cell-monocyte interaction in the production of colony-stimulating activity.[3] Lactoferrin appears to prevent the stimulus provided by monocytes, probably a soluble factor, which provokes T cells to produce colony-stimulating activity. T cells sensitive to this stimulus express the Ia antigen, but do not appear to be confined to either of the T-cell cohorts designated by monoclonal antibodies OKT4 or OKT8 which, in general, define helper cells and suppressor cells, respectively. Ia antigen was first described in the murine transplantation antigen system, where it was found to be present on certain lymphocytes and monocytes. In humans, the DR antigen system is analogous and may be described as Ia-like. In this report, the term is used to describe the human antigen.

Ia antigen is found on T cells when they are activated or transformed and is not found when the cells are in a resting state. The presence of Ia here suggests that the cells have in some way become receptive and able to respond to the stimulus from monocytes. That this action of monocytes is not a unique effect on T cells is evident in recent work from this same group showing macrophages also inducing colony-stimulatory activity from neonatal skin fibroblasts. This colony-stimulating activity production is again sensitive to inhibition by lactoferrin.[16] Studies in our laboratory show eosinophils also inhibiting feedback of CFU-GM, but the mediator remains to be defined.[17]

The major role of monocytes in controlling myelopoiesis is further emphasized by the regulatory action of a prostaglandin of the E series, prostaglandin E_1, which is itself a product of monocytes. Prostaglandin E has been shown to be an inhibitor of CFU-GM,[18-21] but its effect is complex because it may also stimulate the production of colony-stimulating activity[22] and at the same time inhibit the response of the progenitor cells to its action. Progenitor cells may also express the Ia antigen, and only while expressing it do they appear to be susceptible to inhibiting regulation by prostaglandin E.[23] The presence of this antigen on their surface reflects that these progenitor cells are in S phase, and it may be the state of cell kinetics rather than the surface membrane antigen that dictates sensitivity to prostaglan-

din E. During in vitro incubation, the Ia antigen disappears. Prostaglandin E, in fact, stimulates its reexpression in this setting, making it susceptible to later inhibition by this same soluble factor.[24]

Monocytes also provide another monokine, acidic isoferritin, which regulates CFU-GM. Its activity was first described in specimens of leukemic marrow in which normal progenitor cell growth in vitro was suppressed. It appeared to be a product of leukemic cells[25] but has since been found in preparations of normal marrow and attributed to monocytes.[26] Acidic isoferritin acts directly on the progenitor cell, and does not appear to affect other accessory cells. The target, like that of prostaglandin E_1, appears to be those progenitor cells expressing Ia antigen.[27] Whether the Ia is simply a recognition site for isoferritin or whether it is a nonspecific reflector of susceptibility of the cells to inhibition is not clear. Recent studies in leukemic progenitor cells suggest that the antigen itself is necessary for the inhibitory effect both of prostaglandin E and of acidic isoferritin.[28]

In summary, proliferation of the monomyeloid progenitor cell, the CFU-GM, is regulated by several soluble factors released by monocytes and T cells and by their interaction (Figure 1). A series of feedback steps inhibits growth.

BFU-E Proliferation

Role of Monocytes and T Cells

A similar network surrounds proliferation of the primitive erythroid progenitor cell, the burst-forming unit, or BFU-E. The necessary conditions of culture include a source of burst-promoting activity—required for differentiating and proliferating the BFU-E—and the presence of erythropoietin, which allows maturation to recognizable erythroid cells. Both T cells and monocytes have been shown to produce burst-promoting activity.[29-34] Interaction of these cells, prostaglandin E and isoferritins may be involved in the proliferation of BFU-E. Monocytes and T cells have been shown to interact in producing burst-promoting activity[35,36]; some studies suggest that subsets of T cells have opposing regulatory effects on these progenitors.[37] The soluble mediator, prostaglandin E, differs in its effect on in vitro erythropoiesis vis-à-vis myelopoiesis. It stimulates rather than suppresses growth and differentiation of the BFU-E.[38-40] Although there is some controversy, it does not appear to affect accessory cells producing burst-promoting activity but acts only on the progenitor cells. The target of prostaglandin E seems again to be the Ia-receptive progenitor cell. This stimulatory effect differs from its inhibitory activity on CFU-GM and also contrasts with the parallel inhibition of BFU-E and CFU-GM induced by acidic isoferritin on the Ia-containing progenitor cells.[41]

Thus the erythroid progenitor cell is also regulated by monocytes and T cells interacting or independent in producing burst-promoting activity and in providing a modulating influence on growth or proliferation (Table 1).

Progenitor Cell Growth in Hematopoietic Disorders

Pure Red Cell Aplasia

The sensitivity of these progenitor cells to outside influence is evident in some hematopoietic diseases. In vitro study of progenitor cells from patients with disorders of production has shown an array of possible mechanisms that may affect hematopoiesis. A model for disease of a single progenitor cell is that of pure red cell aplasia in which there is a lack of production of only erythroid elements. In this syndrome the specific abnormality appears to vary with the associated clinical picture. In congenital pure red cell aplasia, most evidence supports a lack of the progenitor cell itself, though suppression by T cells has been suggested.[42,43] In contrast, when pure red cell aplasia is

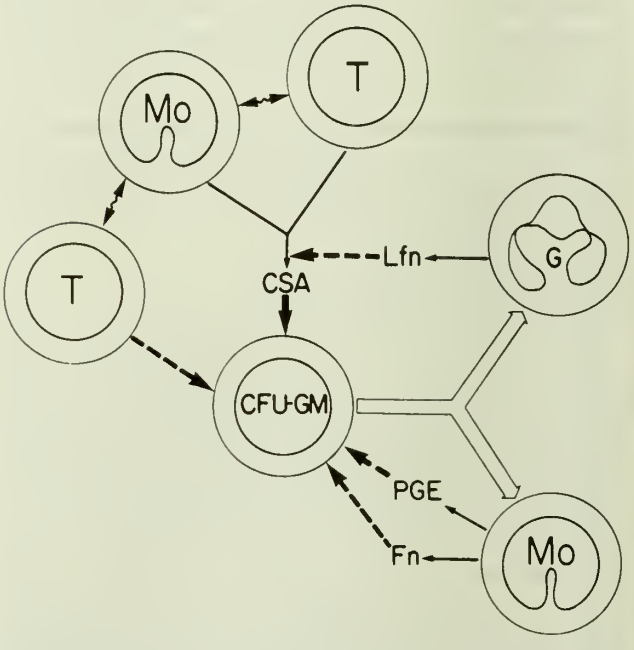

Figure 1.—Cellular control of progenitor cell growth (colony-forming unit for granulocytes and monocytes; CFU-GM). The wavy arrow (◄ ~ ►) indicates interaction between monocytes (Mo) and T cells in producing an effect. The heavy arrow (——►) indicates stimulation and the interrupted arrow (- - - ►) inhibition. The thin arrow (——►) indicates cell products that in turn inhibit or stimulate. Lactoferrin (Lfn) inhibits colony-stimulating activity (CSA) production; isoferritin (Fn) inhibits progenitor cells; colony-stimulating activity stimulates progenitor cells. PGE = prostaglandin E, G = granulocyte

TABLE 1.—*Effect of Cells and Cell Products on Progenitor Cells*

	CSA Production	*CFU-GM Proliferation*	*BPA Production*	*BFU-E Proliferation*
Monocyte	+	..	+	..
T cell	+	+ or −	+	+ or −
Prostaglandin E	+	−	..	+
Isoferritin	..	−	..	−
Lactoferrin	−	..	..	..

+ = increases, − = decreases, CSA = colony-stimulating activity, CFU-GM = colony-forming unit for granulocytes and monocytes, BPA = burst-promoting activity, BFU-E = burst-forming unit for erythroid series.

associated with the lymphoproliferative disorder, progenitor cells may be present, but accessory cells are at fault.[44] In the latter cases, production of burst-promoting activity by T cells is diminished. Following treatment of the lymphoproliferative disorder in these patients with associated remission of pure red cell aplasia, burst-promoting activity production in the presence of T cells is restored to normal. In some cases, a cellular inhibitor of the more mature erythroid progenitor, CFU-E, has also been described and appears to fall in the T-cell cohort.[45] Genetically restricted suppression of BFU-E by the leukemic cells has been found in a patient with pure red cell aplasia and a T-cell lymphoproliferative syndrome.[46] Whether such inhibitory cells are an expansion of a normal inhibitory cohort or an autoimmune response is not known, but the effect diminishes with chemotherapy for the lymphoproliferative disorder.

In cases of idiopathic acquired pure red cell aplasia, autoimmunity has been demonstrated.[44,47] A circulating immune globulin has been found to inhibit BFU-E growth in the presence of complement in such cases. The target cell for this immunoreaction has not been precisely identified and could be either a progenitor or an accessory cell. In these cases progenitor cells and accessory cells function normally when the patient's serum is removed from the system. Again, successful treatment of the syndrome is associated with normal results of in vitro culture in the presence of the patient's serum.

Infection

In patients with anemia associated with histoplasmosis, Zanjani and colleagues have described suppression of erythroid colony growth in the presence of marrow macrophages.[48] Moreover, they were able to attribute the effect to a soluble factor released upon incubation of monocytes. Following cure of the disease, the inhibitory activity could no longer be shown. One may postulate that this is a model for the anemia of chronic disease, in which there may be an abnormality in monokine production—that is, acidic isoferritin—or in monocyte-T cell interaction, resulting in suppression of progenitor cell growth.

Neutropenia

In vitro studies have also provided insight into the possible pathogenesis in cases of neutropenia. T lymphocytes have been identified as a source of inhibition in some cases,[49,50] but B cells may also play a role by producing antibody to CFU-GM.[51-52] In most reports, in vitro studies have been carried out using bone marrow or peripheral blood mononuclear cells, rather than isolated cohorts of cells. Evidence for inhibition is provided by observing the effect on progenitor cell proliferation of removing or adding T cells. One might postulate that the inhibitory action of these T cells is directed toward the progenitor cell itself, or, instead, toward another accessory cell in the regulatory network. Suppression of CFU-GM by T cells could be due to an imbalance of physiologic forces or to a pathologic autoimmune mechanism. In one case of neutropenia associated with tuberculosis described by Bagby and Gilbert, suppression of CFU-GM by T cells was no longer evident after cure of the disease.[49] Evidence for autoimmunity is more clear-cut in those cases in which a circulating immune globulin rather than a T-cell cohort has inhibited CFU-GM growth.

Aplastic Anemia

Aplastic anemia also shows varied in vitro culture characteristics, which suggest multiple causes. In many cases, a cell culture shows simply a lack of progenitor cells. In some, however, the proliferation of CFU-GM or BFU-E is improved when autologous T cells are removed, suggesting inhibition by these T cells.[53-55] In these cases, co-culture experiments in which a patient's T cells are added to normal progenitor cells and vice versa suggest that patients' T cells are inhibitory to normal progenitor cells as well. One must interpret such co-culture experiments with caution, however, because previous exposure to blood products in the patient may result in a cellular immune response that could include cytotoxic response to donor progenitor cells.[55] Few studies have been carried out to identify the subset of T cells involved in progenitor cell inhibition, but it appears not to be confined to the suppressor cell fraction as defined by an OKT8 antigen.

Leukemia

Regulators may also play a role in suppressing normal myelopoiesis and erythropoiesis in leukemia. The relative insensitivity of leukemia progenitor cells to inhibition by acidic isoferritins, the leukemic inhibitory activity of Broxmeyer,[25] may give the malignant cells a growth advantage over normal progenitor cells. Similarly, the myeloid progenitors in cases of chronic myelocytic leukemia are less sensitive than those in normal persons to the "physiologic" inhibitory effect of prostaglandin,[22] a fact that could account for replacement of normal marrow with leukemic clones in this disease.

In cases of acute leukemia, in vitro growth characteristics of progenitor cells are abnormal. In the few colonies present, blast cells predominate and most of the growth is confined to small clusters. Differentiation is lacking. In preleukemic states, alteration of growth characteristics may evolve during the period of observation.[56] These in vitro abnormalities appear to correlate with the aggressiveness of the underlying process and may be the harbinger of leukemic transformation.

Hypereosinophilic Syndrome

In cases of proliferative disease, one might postulate an atypical response to normal regulators or modulation of growth induced by a shift in regulatory activity. In some cases of hypereosinophilic syndrome, the mononuclear cells have stimulated the production of an increased proportion of eosinophils. In other cases, an increased proportion of progenitors committed to eosinophilic differentiation has been described.[57] While these findings may be epiphenomena of this complex

TABLE 2.—*Possible Mechanisms of Deficient Hematopoiesis*

Decreased number of progenitor cells
Inadequate network of accessory cells
Inappropriate suppression by regulatory cells
Autoimmune suppression via cytotoxicity or antibody
Impaired production of stimulatory factors
Selective advantage of abnormal cells not subject to feedback inhibition

syndrome, the results of in vitro studies in this syndrome suggest a role in vivo for the cellular regulatory network.

Thus, in vitro culture of progenitor cells from patients with disorders of the marrow may reveal disturbances in the regulation of their growth. These disturbances may reflect abnormalities in the interaction among accessory cells, both monocytes and T cells, or insensitivity of progenitors to the physiologic regulators involved. In some cases data suggest that an imbalance of normal regulator cells may induce suppression of progenitor cells; in others, the inhibitory effect is consistent with cellular autoimmunity (Table 2). Such studies may give insight into an underlying disease process and can provide a rationale for the treatment selected.

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Epitomes

Important Advances in Clinical Medicine

Pathology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.

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Assessing Fetal Lung Maturity

OBSTETRICIANS are frequently faced with the decision to prevent premature delivery in a case of pregnancy complicated by premature labor. To this end, tocolytic agents are used such as the β-mimetic group, which may produce severe maternal side effects not directly related to dose or length of administration. These decisions to inhibit delivery must balance the possibility of newborn pulmonary distress due to lung immaturity against the risks of maternal-fetal injury or death by the labor-inhibiting therapy. Because the neonatal outcome is so closely linked to prematurity and lung function, a knowledge of fetal lung maturity is of paramount importance.

It is well established that fetal pulmonary maturation is closely related to surfactant lining the alveoli. Without adequate surfactant, immature alveoli collapse when exposed to air, and diffuse atelectasis leads to a respiratory distress syndrome. With amniotic fluid being in continuity with the lungs, it is possible to sample amniotic fluid to measure the pulmonary surfactant. The major components of pulmonary surfactants are phospholipids, predominantly lecithin. Because the maturation process involves a change from predominant amounts of sphingomyelin (which is a poor surfactant) to predominant amounts of lecithin (a good surfactant), the ratio of lecithin to sphingomyelin (L:S ratio) is a useful predictor of fetal maturity. Determination of the L:S ratio has been used for more than a decade since its introduction by Gluck and is still considered the most reliable test for assessing fetal lung maturity. More recently Gluck has augmented this test by measuring the percentage of desaturated lecithin and estimating the quantity of another important phospholipid—phosphatidylglycerol. This complex of tests (L:S ratio, phosphatidylglycerol and percent saturation of lecithin) is done in many laboratories serving obstetric services and is known as a "fetal lung profile."

The reliability of the lecithin-sphingomyelin ratio may be compromised by a number of factors, such as contamination of amniotic fluid by blood, meconium or vaginal secretions. Several maternal diseases have been reported to affect L:S ratios such as diabetes mellitus, sickle cell disease, severe toxemia, primary placental diseases and premature rupture of the membranes. The site of amniocentesis (distance from the fetal mouth) has also been reported to affect the L:S ratio results.

Fetal lung profiles require a thin-layer chromatography procedure that needs considerable technologic skill and at least three hours to do—both drawbacks in the middle of the night. Therefore, recent developments have been directed toward simplicity and rapid performance.

A recent adaptation of the "foam test" has become available commercially. The Foam Stability Index (FSI, SmithKline Beckman Company, Brea, Calif) provides a cassette with seven tubes containing various amounts of alcohol, with one tube being a control. The test has the advantage of simplicity and rapidity; however, the results are discontinuous and semiquantitative.

A rapid immunologic semiquantitative agglutination test for determining the presence of phosphatidylglycerol has recently become available. This test can be rapidly run but again is semiquantitative. In the fetal lung profile, the phosphatidylglycerol determination is quite specific for detecting respiratory distress syndrome, but its sensitivity is relatively low.

Clinical trials of an instrument measuring micro-

viscosity by fluorescence polarization have produced encouraging results, but it is still too early to be sure of the full clinical usefulness of either microviscosimetry, foam stability index or immunologic phosphatidylglycerol. Until there is more validation of these tests, the L:S ratio supplemented by phosphatidylglycerol determination and percent saturation of lecithin will continue to be the reference methods for assessing fetal lung maturity.

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Asbestosis

ASBESTOSIS is an occupationally induced, fibrosing lung disease caused by inhalation of asbestos fibers. Industry is now controlling exposures to asbestos more rigidly than in the past. However, the long latency of 10 to 30 years before asbestosis becomes manifest and uncertainty about the adequacy of control measures mean that the disease will remain for some time. Epidemiologic studies indicate that asbestosis progresses more rapidly in persons who smoke cigarettes or have certain endogenous inflammatory factors (antinuclear factor and rheumatoid factor). Curiously, persons with asbestosis often have cutaneous anergy to tuberculin and other antigens with cell-mediated responses. Nevertheless, clinically significant asbestosis occurs less frequently than other asbestos-related diseases. Malignant mesothelioma and lung cancer are often associated with asbestosis. Their possible asbestos-related cause has stimulated interest in using the early occurrence of asbestosis to confirm suspected exposure to asbestos. Early asbestosis can be diagnosed by scanning iron-stained sections of inflation-fixed lung for clusters of asbestos bodies in areas of fibrosis.

Evidence from several disciplines suggests that fibrosis develops first in the peribronchiolar region. Results of pulmonary function tests indicate obstruction, thought to be in small airways; experimental work in animals shows an early fibrosis around bronchioles, and quantification of fibrosis postmortem in persons with heavy asbestos exposure shows bronchiolar fibrosis. The early fibrotic lesion has been clearly linked to asbestos through measurements of the asbestos fiber burden in the lung by electron optical techniques, including transmission electron microscopy, electron diffraction and x-ray spectroscopy. In cases of asbestosis, an increase in the long, thin amphibole fibers, amosite and crocidolite, is positively correlated with an increase in the degree of fibrosis, whereas an increase in chrysotile, the fiber type most often used in the United States, is not. Whether this is because less chrysotile is inhaled or because chrysotile is more rapidly cleared from the lung than amosite and crocidolite is not clear. Asbestos bodies, visible by light microscopy, are a poor marker of asbestos burden. Their numbers reflect the concentrations of amosite and crocidolite fibers to some degree, but not the concentration of chrysotile fibers, which are generally too short to become coated with the iron-protein coat.

Epidemiologic surveys suggest that exposure to asbestos is a risk factor for lung cancer if asbestosis is present. In this country, only 25% to 50% of cases of mesothelioma are considered asbestos-related, based on a history of exposure and the presence of asbestos bodies and fibrosis in histologic sections. Because exposure to asbestos is often forgotten and does not always result in asbestosis, quantification of asbestos fibers may in the future show an unsuspected exposure in a higher percentage of cases of mesothelioma.

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Cervical Warts

COLPOSCOPY HAS PROVIDED significant new information about cervical warts. It is now widely recognized that, in addition to the classic papillomatous form (condyloma acuminatum), there are three other forms of cervical condyloma: flat, the most common form; the slightly raised form with asperities, and condylomatous cervicovaginitis with myriads of asperities. The distinct histopathologic and cytopathologic features of cervical condylomas have been well recognized since 1956, with the discovery of the hollow epithelial cells, the so-called koilocytes.

In viral, electron-microscopic and immunoperoxidase studies the human papillomavirus has been present in all forms of cervical condyloma. This DNA virus has epithelial affinity, belongs to the family of papovaviruses and has seven subtypes, the most common being type 6.

While the morphologic characteristics of human papillomavirus infection have long been recognized, its frequent association with various forms of cervical dysplasia (cervical intraepithelial neoplasia) has been studied only recently. By immunoperoxidase techniques, the human papillomavirus antigen was detected in 60% to 70% of mild and moderate dysplastic lesions (cervical intraepithelial neoplasia types I and II) and in a lower percentage of the more severe dysplastic lesions that lead to carcinoma in situ. The striking association of papillomavirus-induced cellular changes with forms of dysplasia that lead to carcinoma in situ raises the question of the virus's role in causing cancer.

According to statistical surveys, the incidence of cervical condylomas almost doubled in the decade from 1970 to 1980. The epidemiology of these cases shows

a pattern typical of venereal disease, and it is well documented that human papillomavirus infection develops in two thirds of those who have intercourse with a partner who has genital warts. The mean incubation period is three months. In one study, condylomas were found in 19% of cervical biopsy specimens, and some form of dysplasia was found in 43% of the specimens with condylomas. Condylomas were present in 30% of the 146 cases with dysplasia. The mean age of patients with only dysplasia was 31 years but it was 24 years for those with dysplasia and condyloma.

Data suggesting that papillomavirus-induced cervical lesions may lead to cancer are rapidly accumulating. In an editorial recently the importance of caution in interpreting these lesions was emphasized. The authors concluded that "women bearing the virus-associated lesions should receive the same clinical and colposcopic evaluation, treatment and follow-up as usually administered to women with conventional forms of cervical intraepithelial neoplasia until more data on the natural history of these lesions are obtained."

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Tumor Markers

A MAJOR GOAL in the war on cancer is to advance the time that malignancy is first diagnosed so that effective treatment can be instituted earlier. Pathologists are aware of histologic "markers" of malignancy and note that the cellular order of cancer is less differentiated and more like fetal tissue than is the structure of normal adult tissue. It is not surprising that tumors also often produce fetal products including proteins, enzymes, hormones, serum components, cell surface glycoproteins or cytoplasmic constituents that are characteristic of less differentiated tissue. Measurement of the serum concentrations of these "oncodevelopmental" markers in selected instances has been useful for diagnosis, prognosis and determination of the effectiveness of therapy. Immune labeling of tissue sections is useful for determining the origin of certain cancer cells, and radiolabeled antibodies to tumor markers are used to locate tumors in vivo by radioimmunoscintigraphy. More recently, antibodies to tumor markers have been administered to patients for passive immunotherapy, and experimentally the effectiveness of this procedure is increased by coupling toxic molecules, such as the α-chain of ricin, to the antibody.

The first cancer marker was recognized by a British physician, McIntire, in 1846. This became known as Bence-Jones protein in honor of Dr H. Bence-Jones, who noted the association of this protein with a bone disease then known as "mollities ossium" and now called multiple myeloma. More than 100 years later, this protein, which precipitates in the urine of affected patients when the urine is heated at acid pH, was identified as an immunoglobulin light chain. During the past 20 years, many other tumor markers have been identified, such as carcinoembryonic antigen, α-fetoprotein, pancreatic oncofetal antigen, prostate-specific antigen, melanoma antigens, glial fibrillary protein and other nerve cell products as well as excess or ectopic hormone production, production of enzymes or isozymes, keratin, cytoplasmic proteins and connective tissue components. In a limited number of cases, production of a biologically active molecule such as a hormone may result in symptoms ("paraendocrine syndrome") that may call attention to the possibility of production by a tumor.

At present, a number of new markers is being identified by monoclonal antibodies. The high specificity of this generation of reagents may permit much more precise diagnosis. In addition, monoclonal antibodies may open the door to more specific immune therapy by passive transfer. In anecdotal reports such an approach has shown positive results in selected patients. Broad clinical trials are now under way.

The increasing availability of molecular probes for DNA or RNA sequences or rearrangements associated with cancer may ultimately provide new diagnostic approaches not now available. About 50% of tissues from hepatocellular carcinoma contain hepatitis B virus DNA, and several animal "oncogenes" have been identified in human cancers. It is possible that probes for such structures or for gene rearrangements may replace histologic examination as the major diagnostic tool for differentiating normal and cancerous tissue. For the foreseeable future, however, definitive cancer diagnosis depends on pathologic examination of a tissue specimen, and tumor markers remain useful adjuncts for tumor diagnosis.

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Prognostic Features and the Management of Cutaneous Malignant Melanoma

DURING THE PAST DECADE one of the major advances in the management of malignant melanoma has been the ability to distinguish two categories of patients: those unlikely to experience recurrence or spread (low-risk primary) and those with significant risk (high-risk primary).

The criteria of these two categories include both clinical and histologic factors. The most important histologic feature is tumor thickness measured in millimeters from the skin or ulcerated surface to the deepest area of invasion. Tumors less than 0.76 mm are of low risk and those greater than 1.5 mm are of high risk. Additional factors include the mitotic index, vascular invasion and microsatellites. Clinical factors must also be evaluated in assessing risk. Sex and site are major

prognostic indicators—the prognosis for women is significantly better than for men for virtually all anatomic sites and the anatomic site as a prognostic factor varies from least risk (extremities) to greatest risk (head and neck), with the trunk posing an intermediate risk. The designations low-risk primary and high-risk primary are applicable only to the most common forms of cutaneous malignant melanoma—that is, superficial spreading and nodular types—which together constitute about 85% of cutaneous malignant melanomas. Unusual variants or unclassifiable primaries cannot presently be evaluated for risk of recurrence or spread, and microstage measurements with risk factors are used only for research purposes in such cases.

Current "standard" therapy for patients with malignant melanoma presenting in clinical stage I (primary excised, no evidence of metastasis) has been reexcision of the primary site to prevent local recurrence. Such patients have an overall five-year survival of about 80%, a better survival than with most forms of cancer. The prognosis for the low-risk-primary group is a better than 98% five-year survival. Patients with a low-risk primary can be treated with *conservative* reexcision (about a 1-cm radius) of the primary tumor site without risk of local recurrence. Patients with high-risk primaries have a prognosis directly related to their risk factors. Such patients may need a more extensive surgical procedure, including wider reexcision and perhaps elective lymph node dissection. The margins of surgical reexcisions are becoming more conservative, and elective node dissections are done less frequently, as findings from large patient populations continue to question the necessity or benefit of such procedures. Reexcisions requiring a graft for closure should be unnecessary in most cases and should not be undertaken as standard therapy for malignant melanoma per se.

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Sexually Transmitted Gastrointestinal Tract Diseases

SEXUALLY TRANSMITTED gastrointestinal tract diseases in homosexual men encompass a number of protozoal, helminthic, viral, bacterial and chlamydial infections. Though several agents may be present simultaneously in one patient, not all of the infections may be symptomatic, but rather represent a carrier state. Most infections cause a nonspecific inflammatory reaction. The intestinal mucosa shows neutrophils in the lamina propria, increased numbers of lymphocytes or plasma cells and occasional crypt abscesses. There are some characteristic findings, however, that can be helpful in making a specific diagnosis. For example, *Giardia* and *Cryptosporidium* predominate in small bowel diseases. The latter organism on hematoxylin-eosin stain appears as a small, round, blue organism (3 to 7 microns) on the microvillous surface. These organisms stain blue with Giemsa. Periodic acid-Schiff and methenamine silver stains are not helpful because both react with mucins at the cell surface.

Viral inclusions should be diligently sought in colonic biopsy specimens, but are not always identified in culture-positive patients. Multinucleate cells and perivascular lymphocytic cuffing have been described with herpes simplex virus. Cytomegalovirus inclusions, nuclear and cytoplasmic types, can be seen in vascular endothelium, in cells in the lamina propria and in epithelium. Parasites such as *Entamoeba histolytica, Strongyloides, Trichuris* and even *Cryptosporidium* may be seen. If the biopsy specimen is from the rectum and if a prominent plasma cell infiltrate or multinucleate giant cells are seen, syphilis (plasma cells) or chlamydial infection (giant cells) should be looked for. These, as well as other bacteria—such as *Yersinia, Campylobacter, Neisseria, Salmonella* and *Shigella*—may simply cause nonspecific findings. Finally, hepatitis B can be sexually transmitted, and hepatitis A is probably transmitted by this route.

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Secondary Diseases in Immunosuppressed Patients

NORMAL FUNCTION of the human immune system requires the interaction of multiple independent cell lines derived from a common pluripotent hematopoietic stem cell. The most important of these cell lines are the T and B lymphocytes and the phagocytes (macrophages and neutrophils). The B lymphocytes produce the specific antibodies required for humoral immunity, the T lymphocytes are primarily responsible for cell-mediated immunity and the macrophages process antigen in addition to their function as phagocytes.

Immune deficiencies may be congenital, iatrogenic or acquired. Patients with these disorders all show unusual susceptibility to infections and have an increased incidence of malignancy. The types of infections are, in a general way, predictive of the portion of the immune system involved. In patients with defects in humoral immunity, or neutropenia, recurrent infections with pyogenic bacteria tend to develop. Defects in cell-mediated immunity frequently result in disseminated viral, fungal and protozoan *(Pneumocystis carinii)* infections. Because of the complicated interactions of the immune system, patients with humoral immune defects may also have problems with viral infections and, conversely, overwhelming bacterial infections may develop

in patients with cell-mediated immune deficits. The most common malignant conditions in which immune deficiency states develop are malignant lymphomas, both Hodgkin's and non-Hodgkin's. Acute leukemias also occur, and the incidence of Kaposi's sarcoma in the recently described acquired immune deficiency syndrome (AIDS) is striking. Other malignant conditions occur but are not increased in incidence above the normal population.

Congenital immunodeficiency states are rare disorders that generally present in childhood, whereas the iatrogenic forms are generally a result of aggressive therapy for malignancy or immunosuppression for transplantation. Until recently, clinically significant acquired immunodeficiency was uncommon; the recent outbreak of AIDS has changed that in many parts of the country.

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Cytomegalovirus Infections in Infants

CYTOMEGALIC INCLUSION DISEASE is an infection due to cytomegalovirus, a herpesvirus originally called salivary gland virus. This virus can produce a localized infection, affecting most commonly the gastrointestinal and respiratory tracts, or a generalized infection in which almost any organ may be involved. Histologically, a fairly typical eosinophilic intranuclear inclusion with a clear halo ("owl's eye") can be identified in affected tissues. Occasionally basophilic cytoplasmic granulations are also found.

Infants may acquire the disease in utero, during birth by contamination from the genital canal or by becoming exposed to the virus shortly after birth from sources such as breast milk, tears or other secretions. The infants who appear to be at greater risk are those born to mothers who have acquired a primary infection during gestation.

It is estimated that 0.5% to 2% of the neonates are excreting the virus and that, of these, major complications including central nervous system damage will eventually develop in a significant percentage (10% to 20%). Cytomegalovirus is the most common cause of viral-induced psychomotor retardation. Isolating infants known to be excreting the virus from schools or playgrounds is not practical since many nonidentified children are also excreting the virus.

The most specific and sensitive method for diagnosing a case of cytomegalovirus infection is isolating the virus from tissues, urine, saliva or other body fluids. Detection of IgG antibodies in an infant's blood specimen should be interpreted only in parallel with the mother's IgG antibodies because there is transplacental transfer of this type of antibodies from the mother to the fetus. IgM antibodies do not cross the placenta, but technical problems limit the diagnostic usefulness of routinely measuring their levels.

Vaccines, interferon and several drugs such as acyclovir have been evaluated for the prevention and treatment of cytomegalovirus infections. Although some encouraging results have been obtained, we do not yet have an effective method for controlling this disease.

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The Role of Coronary Collateral Arteries in Myocardial Ischemia

THE QUESTIONS whether well-developed coronary collateral arteries afford protection to an ischemic myocardium and whether various interventions such as exercise and pharmacologic agents promote collateral development have been studied in numerous experiments. The equivocal findings reflected the great variation in the number of naturally occurring collateral vessels in animals. Recent studies have been conducted in an animal model that has sparse, innate collaterals and a response to exercise stress similar to that seen in humans.

The effects of exercise on collateral development in myocardial ischemia were studied in pigs subjected to critical coronary artery stenosis and then given exercise training. After five months the exercise-trained animals had a greater increase in coronary collateral flow and smaller infarct sizes than their matched sedentary controls. These findings showed that development of the coronary collateral circulation and myocardial tissue salvage are enhanced by exercise training. Thus, exercise during an evolving infarct is effective as an augmentation to collateral growth but is not without risk. If embarked on, it should be conducted only under rigid medical supervision.

The effects of daily aspirin administration on collateral vessel development in cases of myocardial ischemia were studied in pigs subjected to gradual occlusion of a major coronary artery by an Ameroid constrictor. Coronary collateral blood flows were measured at rest and during exercise stress at three days and two months after coronary artery occlusion. The aspirin-treated animals had greater collateral blood flow during exercise stress (61% versus 45% of control; $P<.001$), smaller myocardial infarcts at autopsy (18% versus 32% of the myocardium at risk; $P<.001$) and more prominent collateral development on gross and histologic examinations.

The results of these studies indicate that in an animal

with sparse innate coronary collateral vessels similar to those in humans, certain interventions can promote coronary collateral artery development and potentially protect ischemic myocardium by salvaging tissue in the jeopardized zone and reducing infarct size.

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The Flow Cytometer in the Clinical Laboratory

FLOW CYTOMETRY involves passing a beam of laser light through a stream of cells and then analyzing the scattered light in relation to the number of cells stained by one or more fluorescent probes. This technique has been used for at least ten years in research laboratories to separate out specific cell populations and to analyze cells and cell populations with respect to surface antibody staining or DNA staining or both.

There are significant advantages to the use of the flow cytometer. Fluorescence microscopy seldom allows for the quantitative measurement of the staining properties of each individual cell, and becomes a very laborious process if more than a few hundred cells are to be analyzed. In addition, bulk measurements of collections of cells give average results for the overall population and do not really delineate possible subpopulations that often exist in lymphomas, for example. Flow cytometry, on the other hand, allows for the rapid and quantitative measurement of thousands of cells and multiple properties of each. For example, DNA content and cell size can be used as criteria for the detection of abnormal populations of malignant cells. It has been shown that hyperdiploid cells can easily be distinguished from their normal counterparts by determining both the size and the DNA content of the cells. Braylan and colleagues have recently used the simultaneous measurement of DNA content and surface markers to define abnormal cell populations in malignant lymphomas. Because malignant cells are capable of changing during the course of a disease, it is important not to rely solely on one method of identification.

The clinical applications of the flow cytometer are generally restricted at present to the analyses of lymphoma and leukemia lymphocytes. Future application may involve a determination of κ- to λ-chain ratios. The amount of each chain on the surface of normal lymphocytes is about equal, whereas in malignant cells, a change in the ratio of κ- to λ-chains is observed. Other applications will involve the detection of autoantibodies in autoimmune hemolytic anemia, neutropenia and immune thrombocytopenia. Of these potential uses, the most developed at present is the detection of antibodies on platelets. Antiplatelet antibodies can be accurately measured in 1 ml of blood from a patient with a platelet count of 1,000 per μl or less. This determination cannot be done by any of the other techniques currently used because of the significantly larger numbers of platelets required.

The primary drawback of this system is the cost. Most flow cytometers currently used for clinical applications cost in excess of $100,000. For use in only a limited number of tests, most hospitals other than large centers for leukemia or lymphoma would have trouble justifying such a large capital expenditure. A problem specifically associated with such sophisticated equipment is that, in spite of attempts to simplify the mode of operation, a highly trained technician is needed to operate the machine because the likelihood of major breakdowns is quite high. In addition, the rate of cells passing through the machine cannot really be increased above 5,000 cells per second and this is relatively slow if one has to analyze a million cells to get reliable data. This is a serious drawback, and unless there is a basic change in technology, it will remain a major limiting factor.

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Current Trends in Drug Overdose

DRUG AVAILABILITY, price and current fads are mainly responsible for changing trends in drug intoxication. In Los Angeles, phencyclidine hydrochloride (PCP) is widely available, relatively cheap and the most popular drug of abuse. The incidence of admissions to hospital for PCP intoxication is correspondingly high. Four PCP analogues with effects similar to PCP are available on the streets.

Cocaine use is rampant, and cases of severe cocaine poisoning are appearing sporadically. Some patients who die in status epilepticus have a ruptured package of cocaine in the bowel at autopsy.

Heroin, a perennial favorite, is presently abundant and down in price. Intravenous injection of heroin mixed with cocaine (a "speed ball") is an old combination regaining its popularity. A new fad is "smoking" heroin by heating it on a piece of aluminum foil and inhaling the vapors. As the drug volatilizes the particles "jump around" on the foil. This practice is called "chasing the dragon." The most popular narcotic appears to be codeine, usually taken in tablets containing either aspirin or acetaminophen. Acetaminophen intoxication remains a common problem.

Two drugs of the 1960s, glutethimide and LSD (lysergic acid diethylamide), have returned. Glutethi-

mide is frequently ingested with acetaminophen and codeine. This combination, called a "Doriden load," is favored by persons with narcotic addiction as a substitute for heroin. Glutethimide overdoses are often life-threatening. LSD is impregnated on postage-stamp-size colored pictures printed sequentially on transparent plastic ("transfers") or white porous paper ("blotters"). Drug abusers lick these "papers," transfer the picture to their skin and experience LSD intoxication. LSD is also poured over small pieces of pasta for street sale.

The preferred hallucinogen for "new wave rockers" is MDA (methylenedioxyamphetamine), which may be sold as very small—about 4 by 6 mm—flat, rectangular transparent chips of crystallized material called "window panes."

The use of amphetamines, including "look-a-likes" containing caffeine or phenylpropanolamine, is increasing, especially that of crystalline methamphetamine called "crank."

Intoxication from various sleeping pills and benzodiazepines continues. The leading cause of intoxication is still ethanol alone or in combination with another drug.

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Fine-Needle Aspiration Biopsy of the Prostate Gland

FINE-NEEDLE ASPIRATION has been used as a diagnostic tool since the beginning of this century. A mildly invasive technique, it has grown in popularity in the United States primarily on the basis of the ease and accuracy with which it can be used to obtain biopsy specimens to diagnose lesions in breast, superficial lymph nodes and thyroid. The prostate, however, is not so readily accessible and fine-needle aspiration of masses in this organ has not gained so ready an acceptance. After ten years' experience of doing this procedure on superficial lesions at the Karolinska Hospital in Stockholm, Dr Sixten Franzen in 1960 constructed a needle guide that makes the prostate easy to reach through the rectum using a 22-gauge needle.

The use of fine-needle aspiration is indicated when there is a suspicious, palpable lesion in a prostate. If a patient presents with distant metastasis for which the prostate may have been the source of the primary lesion, random aspirations of the four quadrants of the gland can be done. Not infrequently, such quadrant biopsy specimens will confirm the diagnosis of prostatic carcinoma. Lesions of clinically apparent prostatitis should not be aspirated.

With the Franzen needle guide, specimens can be taken of even very small (about 0.5 cm) and superficial lesions with a high degree of accuracy. Specimens from several different areas of the prostate can be taken without significant hemorrhage or other side effects. Fine-needle aspiration of the prostate is an outpatient procedure and does not require anesthesia. Patient discomfort is minimal, and patients readily accept a repeat biopsy if it is required.

In contrast, a core biopsy specimen obtained with a cutting needle requires local or general anesthesia and is less accurate, especially for small and superficial lesions in the posterior portion of the prostate. The sections from a core biopsy show only a fraction of the cells present in the specimen. An aspirate specimen almost always shows more cells for study than does that from core biopsy. In general, cellular detail on cytologic preparations from fine-needle aspiration is superior to the paraffin-embedded sections of a core biopsy.

The main disadvantage of this procedure is that there is a shortage of physicians in this country experienced in the biopsy technique and in the interpretation of the resultant smears. Good results cannot be obtained through reading about the technique and then attempting to do it; fine-needle aspiration must be learned under supervision, and the smears should be examined to ensure adequacy of the material.

After acquiring sufficient skill in the technique, it is still necessary to do at least five to ten aspirations a week. This is about the same degree of experience necessary to maintain skills in microscopic interpretation. Optimal results are obtained if the same physician does the aspiration and interprets the slides.

When performed and interpreted by a trained physician, fine-needle aspiration of the prostate gland is a highly accurate, fast and minimally invasive biopsy technique. There is a great need in this country for training programs to instruct physicians in the techniques of fine-needle aspiration of the prostate gland and other organs. If trained physicians are unavailable, it is better to rely on traditional histologic techniques. During the transition period between the use of traditional (core) biopsy and the implementation of fine-needle aspiration techniques, it may be feasible to do both procedures until such time as enough experience with the aspiration technique has been gained.

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Hepatitis—δ-Agent

THE RECENT DISCOVERY of a new hepatitis agent called delta (δ) marks the most exciting milestone since the identification of hepatitis A and B viruses nearly two decades ago. The δ-agent is a defective RNA virus, thus a virus taxonomically distinct from the hepatitis B virus (HBV) but requiring helper functions supplied by HBV. Hence, δ-hepatitis can occur *only* in the presence of HBV, and has three clinically recognizable forms: concomitant acute B and acute δ-hepatitis,

superinfection by the δ-agent in persons who are hepatitis B carriers and chronic δ-infection in a patient who has chronic hepatitis B.

Although simultaneous acute B and δ-infections can present as ordinary acute hepatitis, more often this dual infection results in a severe fulminant form.

δ-Superinfection in an HBV carrier may occasionally result in fulminant hepatitis but usually manifests itself as an acute icteric illness that is followed by chronic progressive liver disease. We now realize that the clinically evident, recurrent, hepatitis-like illness accompanied by jaundice that became more common during the late 1960s, which we all called chronic active hepatitis, was principally δ-modified chronic active hepatitis B. Data now show that, at least in the Los Angeles area, 82% of drug users with chronic active hepatitis B also have δ-infection.

Our clinical colleagues have noticed a difference in the manifestations of chronic active hepatitis in drug users as compared with ostensibly the same disease in homosexual men or in Asian immigrants. Similarly, we have been impressed with the general difference in "aggressiveness" of the hepatic histologic patterns in drug users versus nonusers who have chronic active viral hepatitis B. A major difference has been the presence of δ-superinfection, common in the former and uncommon (but increasing!) in the latter. It is likely that the histologic features of chronic active viral hepatitis that most pathologists have learned actually represent the dual infection. Serologic tests for δ-antibodies and immunologic staining for δ-antigen in the liver tissues establish the clinical diagnosis.

The δ-infection is described as endemic in Italy and sporadic in worldwide distribution. A major outbreak of cases of severe hepatitis due to δ-infection recently reported from South America should alert physicians to test for δ-markers in any new outbreaks of severe hepatitis.

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LD_6—A Biochemical Sign of Impending Death

AN EXTRA isoenzyme band of lactate dehydrogenase (LD) (EC 1.1.1.27) that is cathodic to LD_5 has been identified by several investigators. The underlying clinical condition is arteriosclerotic cardiovascular disease causing congestive heart failure with massive congestion of the major viscera. All of the patients had elevated total LD and creatine kinase (CK) levels. Serum enzyme electrophoresis showed that the LD_1 level exceeded or was equal to LD_2 and the CK-MB level was increased more than 5% as the acute myocardial infarcts evolved. As congestive heart failure became evident, a prominent amount of LD_5 became apparent, as did an LD_6 isoenzyme band cathodic to the LD_5 isoenzyme band. The ratio of blood urea nitrogen to creatinine was greater than 10:1 due to the progressive prerenal azotemia.

LD_6 is extremely stable at 56°C, 4°C and 25°C. It is not bound to an immunoglobulin and does not contain an H (myocardial) monomer but does contain an M (skeletal muscle) monomer. It may represent a posttranslationally modified LD_5.

LD_6 is not an artifact and most likely should be metabolized and cleared by a healthy liver and kidney. It is present and is identified when there is ischemia of the liver and kidney with circulatory failure. The appearance of LD_6 portends a very poor prognosis—as does the presence of creatine kinase mitochondrial isoenzyme—and is a sign of impending death.

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Heparin-Induced Thrombocytopenia and Thrombosis

DESPITE THE FACT that heparin is a powerful anticoagulant, it will infrequently induce thrombocytopenia and thromboembolic complications. Heparin-induced thrombocytopenia typically occurs about eight days after the institution of heparin therapy and is frequently followed by deep vein thrombosis, pulmonary embolism, arterial thromboembolic complications or a combination of these. Prior periods of heparin therapy will predispose some patients to the development of thrombocytopenia (less than 100,000 platelets per μl) as an anamnestic response within three to five days after reexposure. The episodes of arterial thrombosis or "white clot" syndrome frequently lead to infarction of end organs such as brain or heart or gangrene of an extremity. Although apparently ten times more likely to occur with bovine heparin than with porcine heparin, heparin-induced thrombocytopenia with thrombosis has occurred with both types. There does not appear to be a relationship to dosage, route or frequency of administration. The use of low-molecular-weight porcine heparin in this situation is promising but is still under study.

If the patient survives the thromboembolic complications, the platelet count usually returns to normal within two to four days after cessation of heparin therapy. Most patients who have been rechallenged with heparin after periods varying from a week to one year again manifested immediate thrombocytopenia.

In contrast to heparin-induced thrombocytopenia with thrombosis, there is a benign, mild depression of the platelet count that commonly occurs within two days after the institution of heparin therapy. Poorly understood, this type of heparin-induced thrombocytopenia is not mediated immunologically and requires no treatment. Although the reported incidence of both types of thrombocytopenia together reaches up to 30%,

the incidence of clinically significant heparin-induced thrombocytopenia with thrombosis probably varies between 0.6% and 5%. No risk factors in an unexposed patient have yet been discovered.

Heparin-induced thrombocytopenia with thrombosis does not involve the action of thrombin but is mediated by an IgG antibody that reacts with heparin on the platelet membrane to activate complement. This reaction initiates thromboxane synthesis, which leads to platelet aggregation rather than platelet lysis. Aspirin will block this sequence of activation. This IgG antibody can be detected in most cases of heparin-induced thrombocytopenia with thrombosis by testing for platelet aggregation in the presence of heparin using an aggregometer. In aggregation studies of some affected patients, however, heparin has induced aggregation in vitro only when tested on specimens taken two to three days after cessation of heparin therapy.

The high rates of morbidity and not-infrequent mortality make prevention the treatment of choice. This is usually accomplished by monitoring the platelet count of every patient every two to three days during the first 15 days of heparin therapy. The onset of this condition should always be suspected when a patient shows increasing resistance to heparin, progressive thrombocytopenia, worsening thrombophlebitis despite heparin therapy or new thromboembolic complications during heparin therapy. If the laboratory and clinical findings indicate heparin-induced thrombocytopenia with thrombosis, heparin therapy should be terminated immediately, including any heparin used to maintain the patency of intravenous lines. Antiplatelet agents should be administered and vitamin K antagonists used if needed. A promising role for antiplatelet agents is suggested by a recently reported case of a dialysis patient who had heparin-induced thrombocytopenia with thrombosis who subsequently tolerated heparin well during dialysis by taking aspirin. JEFFREY D. CAO, MD

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Creatine Kinase Isoenzymes

CREATINE KINASE (CK) is an intracellular enzyme that exists as three dimeric isoenzymes; CK-MM, primarily from skeletal muscle; CK-MB, primarily from cardiac muscle, and CK-BB, primarily from brain and smooth muscle. Major interest has focused on developing methods of detecting and quantitating CK-MB in serum because of its diagnostic and prognostic implications in ischemic cardiovascular disease. Because both CK-MB and CK-BB are thermolabile, a laboratory must develop appropriate methods for procuring and storing specimens before analysis to ensure optimum isoenzyme activity. Electrophoresis is widely used to identify and quantitate CK isoenzymes and the only practical method for detecting abnormal variants of CK such as macrocreatine kinase (macro-CK). Ion-exchange chromatography and methods based on selective chemical activation of the MB isoenzyme have also been used. Isotopic and nonisotopic immunoassays are gaining in popularity because of increased sensitivity. It is imperative that each laboratory establish normal ranges and detection limits for the MB (and BB) isoenzyme(s) regardless of the method chosen.

CK-MM activity in serum increases following muscle work, trauma or ischemia. Myopathies also cause variable increases in CK-MM.

The presence of CK-MB in serum was once considered to be synonymous with myocardial infarction. We now know of several other cardiogenic and noncardiogenic causes of CK-MB in serum. However, the characteristic rise and fall of serum CK-MB activity in the proper clinical setting is still an accurate index of myocardial infarction. The isoenzyme appears in serum specimens from 3 to 6 hours after an infarct, peaks at 12 to 24 hours and generally disappears in 48 to 72 hours. Other cardiogenic causes of increased CK-MB activity in serum include cardiac operations, myocardial ischemia, myocarditis and cardiac trauma. Small increases in serum CK-MB activity have occasionally been seen with cardiogenic shock, cardiac catheterization, ventricular tachycardia, defibrillation and following stress testing.

Noncardiac causes of CK-MB activity in serum include myopathies and dystrophies of skeletal muscle, massive skeletal muscle trauma, ischemic and alcoholic rhabdomyolysis, malignant hyperthermia, hypothermia, carbon monoxide poisoning and Reye's syndrome. CK-MB may be found in the serum of neonates. Persistence of CK-MB in adult serum specimens with no apparent cardiac or skeletal muscle disease is rare. Tumor-associated CK-MB has been rarely seen in cases of adenocarcinoma of prostate, colon and lung and of rhabdomyosarcoma.

Several recent reports cite CK-MB activity in serum specimens of marathon runners before, during and after races. CK-MB activity in skeletal muscle of trained long-distance runners is greater than in controls and parallels serum activity. Technetium Tc 99m pyrophosphate scintigrams following marathons show no myocardial uptake but significant uptake in quadriceps muscles that suggests a skeletal muscle source.

CK-BB is rarely detected in serum specimens of adults but is commonly found in cord blood and neonatal serum specimens. CK-BB is frequently seen with cerebral anoxia associated with cardiogenic shock and, transiently, following a cardiopulmonary bypass surgical procedure. Patients who have sustained significant cerebral trauma may manifest serum CK-BB activity. CK-BB activity is seen in serum specimens from postpartum women from five to eight hours after delivery.

Of particular interest is the association of CK-BB with several malignant conditions. Homogenates of many epithelial, lymphoid and glial tumors contain significant CK-BB activity. Tumor-associated serum CK-BB is seen occasionally in cases of small-cell anaplastic carcinoma of pulmonary origin and prostatic adenocarcinoma. Other epithelial tumors may also elaborate this isoenzyme.

Abnormal isoenzymes of creatine kinase may be detected by electrophoresis. Macro-CK is a complex of CK-BB and an autoantibody to CK-BB that may migrate anywhere between CK-MB and a point cathodic to CK-MM. It may confuse interpretation of electrophoretograms and may elute with the MB fraction in chromatography systems, causing a false-positive result. Mitochondrial creatine kinase is another abnormal variant of macro-CK that should not be confused with CK-MB. It is rare and usually seen in gravely ill patients, many of whom have disseminated malignant disorders.

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Fine-Needle Aspiration of the Breast

OPTIMAL FINE-NEEDLE ASPIRATION biopsy of a palpable breast nodule requires three individual but inseparably linked diagnostic steps: biopsy, morphologic evaluation and final clinicopathologic correlation. The initial biopsy phase consists of precisely manually locating and immobilizing the nodule, puncturing the nodule by rapid needle movements with repeated redirection over one to three seconds, expelling the material onto glass slides and delicately spreading (versus smearing) the cells in monolayered sheets on glass slides. Generally, three such biopsy specimens in experienced hands can provide adequate sampling for most breast nodules. Although these intricate movements are detailed by Linsk and Franzen, words and illustrations cannot replace working with someone skilled in the procedure. Suboptimal biopsy technique is more likely to result in failure to diagnose carcinoma than is an inexperienced morphologic interpretation.

Because a specimen from fine-needle aspiration usually consists of clustered epithelial cells without accompanying fibrous stroma, the many criteria in surgical pathology that rely on the relationships between large groups of tumor cells and their accompanying stroma are of little use in this procedure. Fortunately, the excellent fixation afforded to the small aspirated cell groupings and the absence of paraffin-processing artefact common to routine pathology tissue sections render the directly stained fine-needle aspiration smears in crisp and reproducible cytologic detail. Typically, benign breast ductal cells have a small nucleus (about 1½ erythrocyte diameters), uniform nuclear placement and preserved intercellular cohesion. Malignant features are typically the opposite of one or more of these basic benign criteria. The various exceptions and diagnostic nuances can be learned through experience, as can their equivalents in surgical pathology.

The diagnostic features in aspirated material are best assessed in air-dried material processed with one of the metachromatic stains commonly used for hematology, such as Wright's stain. The consistent nuclear diameter and cytoplasmic detail in this fixation-staining system are perfect for three basic breast criteria. Nuclear chromatin detail available in alcohol-fixed and Papanicolaou-stained material, while the cornerstone of "classic" cytologic tests as in cervicovaginal smears, adds little to breast material from fine-needle aspiration. Indeed, the generally limited definition of cytoplasmic features offered by the Papanicolaou stain and the coexisting potential of air-drying artefact before alcohol fixation can be formidable diagnostic hindrances. Hematoxylin and eosin staining, the mainstay of surgical pathology tissue specimens, is undesirable in routine fine-needle breast aspirate for similar reasons.

Like the last movement of a symphony, the clinicopathologic correlation reviews and then develops all preceding information into a final statement. Here the clinical history, physical characteristics of the nodule, pattern of needle resistance, type or quality of material expelled from the needle, adequacy of smears and their staining and the microscopic appearance of these cells are all interwoven by an experienced practitioner to provide the most detailed diagnostic statement possible. In a sense, each needle aspiration biopsy procedure must conclude with the question, Does the material observed on microscopic examination adequately explain all the preceding clinical and gross biopsy findings?

When these three steps are optimally carried out by a trained and experienced physician, the false-negative rate is 2% to 6% and the false-positive rate is about 0.1%, in keeping with frozen-section diagnostic results. In discussions by pathologists and nonpathologists, there is often a tacit assumption that surgical excision diagnosis alone is infallible and provides the only "acceptable" method of diagnosing a palpable breast nodule. In fact, one investigator has shown that the false-negative rate of "benign" surgical pathology material may be as high as 2.4%. Moreover, a surgical pathologist can have false-positive frozen-section results.

If every "significant" breast nodule were to be surgically excised, the preceding discussion as to the relative accuracy of fine-needle aspiration versus surgical excision might be moot. Palpation, which is the common antecedent to surgical excision, is in fact less

sensitive in reliably diagnosing carcinoma than is fine-needle aspiration. In one study the false-negative rates were 10% for palpation and 4% for needle aspiration. Although mammography has a significant role in evaluating nonpalpable breast nodules, its efficiency rate (true-positive plus true-negative results expressed as a fraction of the total population) for palpable nodules is reduced by many noncommittal ("suspicious") diagnoses. Indeed, any test's false-positive and false-negative rates can be reduced to zero if all test results are "suspicious." Under these circumstances, however, the efficiency (or general applicability of the test to broad patient populations) would be zero. Efficiency rates for fine-needle aspiration, palpation and mammography according to one study are 81%, 72% and 58% respectively.

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Editorials

A Protocol for Problem Solving in Health Care

PHYSICIANS HAVE DEVELOPED what is really a remarkable protocol or instrument for problem solving in patient care. It is particularly useful when problems are complex, when the situation is fluid or changing, and when the necessary facts and data may not be readily at hand. It allows for decision making even when information is inadequate or incomplete and has the advantage of providing for course corrections as the situation changes and more information becomes available. The protocol is followed by any physician who must address a complex or puzzling problem in patient care and it is familiar to any medical student by the end of his or her second year of training. It is curious that this time-tested problem solving method has never really been applied systematically to the complex problems of health care generally, especially when the situation is fluid and the necessary facts and data base are not readily at hand.

The protocol of course starts with the chief complaint (in health care this might be the unacceptable escalation of costs, for example); moves on to as accurate a description of the present illness as possible; reviews the past history, social history, occupational history and so forth, to see what bearing, if any, these might have on the illness under consideration. Next there is a system review of the several independent yet interdependent parts of the living system under study to seek clues that may suggest poor or inadequate performance in any of them or any evidence that they may not be working as well together as they should. So much for the history. Then there is the physical examination. The ailing person is actually examined by hands-on methods with special attention to where the trouble seems to be. Findings are described objectively, and where possible measurements are made and recorded. Next, additional objective data are sought through tests and measurements of various kinds to further define the nature and extent of the illness. Persons with special expertise are sought and brought into consultation as needed. In this way both subjective and objective information about the illness and its likely prognosis are carefully acquired.

Based on the above, and however complete or incomplete the subjective and objective information may be, a diagnosis or at least a working diagnosis is identified, and based upon this a treatment plan and a plan for follow-up observations and studies are devised. It is here that a consensus or agreement must be reached among all those that are affected as to whether the diagnosis and treatment plan are reasonable and who is to be responsible for doing what. In patient care this is the point of informed consent on the part of the patient and often the family, and coordination of the treatment plan agreed to among the team of health care providers. When all of this has been accomplished the treatment agreed upon is begun. This may be done rapidly in an emergent situation or may take a relatively long time and require a lot of information in a particularly difficult or puzzling case.

But this is not all. As the treatment proceeds and the situation evolves, signs of change are monitored, measured where possible and incorporated into the diagnosis and treatment plan as soon as they occur, again with the involvement and informed consent of all those concerned, which in these days may include the insurers as well as the patient, the family and the professional and institutional providers of the care.

It is suggested that this format or protocol for problem solving in patient care may have something to contribute to solving some of the larger and equally puzzling problems of health care. Certainly no approach as systematic as this has yet been tried. But the health care enterprise seems to have many of the characteristics of a living system. It is complex, it is changing all the time, it has its own very real homeostasis (which protects it somewhat from onslaughts from both within and without) and it has many independent yet interdependent parts. If the chief complaint now is the "high cost of health care," might this not be addressed following a protocol similar to the one used to address a difficult and complex problem in patient care? The tools to be used would of course be different, but the basic sequence or protocol of a careful history, an objective hands-on examination where the problem is, appropriate data collection, a working diagnosis and treatment plan agreed to by all concerned, provision for continuing evaluation of both diagnosis and treatment and for prompt course corrections as needed, would seem well worth a serious trial. It would be costly, but so is the rising cost of health care. Somehow we need an agreed-upon diagnosis and treatment plan for this and perhaps some other complex problems in health care that are appearing on the scene. As in patient care, agreement and consent by those directly involved tends to facilitate compliance and cooperation in what is seen as a common effort to achieve a common goal. The protocol physicians use in dealing with difficult problems in patient care has stood the test of time. It has a good track record of success. Perhaps it is a diamond in our own back yard.

MSMW

Progress in Orthopedics

AMSTUTZ AND CO-WORKERS admirably detail in the Specialty Conference in this issue the recent advances in orthopedic research, with appropriate special emphasis on the investigative activities of the scientists at the University of California at Los Angeles. Before commenting on some of the points raised by their review, it is important to note some of the remarkable features of the discussion. First is the fact that although all of the research advances in orthopedics included in their summary have direct clinical application, they represent the culmination of extensive basic research by numerous investigators in many centers, some far removed from the clinics and operating rooms. Isolated facts, gleaned from biochemical and bioengineering studies in basic science laboratories, have been applied by the clinical investigators at UCLA and elsewhere to bear on problems of patients, and the solutions now emerging appear to be effective in prolonging life and alleviating suffering.

The second general issue raised by this report is that all of the research reported by the UCLA group is being done by orthopedists. Such a comment would seem gratuitous for many specialties, but for orthopedics, traditionally a "service"-oriented discipline, the shift is not only noteworthy but a source of great pride. If one reviews the changes in orthopedic practice for prior decades, it is evident that such advances as the control of anterior poliomyelitis, tuberculosis and bacterial infections represented the major factors, with orthopedists contributing for the most part only new methods of conservative or operative treatment. The change is important and indicates perhaps the maturation of our discipline, which, despite the long existence of a discrete body of knowledge, has until recently had a limited scientific base. The work so well described by the UCLA group provides ample testimony to the enormous expansion of that scientific base and, perhaps more important, its application to the development of real solutions to clinical problems.

Turning now to a discussion of the individual sections of the UCLA report, Dr Amstutz and his colleagues have described in some detail the advances in the management of osteosarcoma by drugs and limb-sparing surgical procedures; treatment of nonunion of long bones by application of electrical fields; dealing with bone and soft tissue defects by transfer of free flaps using microvascular anastomotic techniques; management of end-stage arthritis by new designs and implantation techniques for joint replacement, and for a finale—a search for the "Holy Grail" of orthopedics—the elusive biochemical factor(s) in bone that induces bone formation.

Limb salvage procedures in the management of primary malignant tumors of the extremities have resulted from a variety of improved management systems for patients afflicted with these rare but devastating diseases. In past years, the survival for patients with osteosarcoma, even with prompt amputative procedures, was less than 20%, but with the use of potent chemotherapeutic regimens, including that reported by Dr Johnson, not only can patients look forward to a longer disease-free survival, but, by the application of improved surgical techniques, undergo a wide local resection of the tumor-bearing tissues, with little threat of local recurrence.

Such surgical procedures are now commonplace in tumor centers but introduce the problems of restoration of skeletal continuity by an appropriate prosthetic or allograft implant that will hold up to the demands of teen-age patients, who are most commonly the ones in whom these tumors are encountered. The dilemma presented by the authors is a real one: custom prosthetic implants are unlikely to endure the demands of active patients, while cadaveric allografts, successful for lower grade lesions, have a high complication rate in patients with osteosarcoma, based partially on the extent of the soft-tissue loss and the need to treat a patient with adjuvant chemotherapy. The authors' approach to chemotherapeutic management of these patients is rigorous and their early results with metallic implants promising. In their center, as well as in others, research continues to improve the likelihood that allograft implants will survive the drug treatment, be accepted by the host tissues and be revascularized in a fashion similar to autograft—theoretically, at least, an ideal solution.

The use of electrical and magnetic fields in the treatment of nonunion or delayed union of bone is the culmination of years of research into the relationship of bone formation to piezoelectrical effects encountered with stress of the semirigid bones. There is now little doubt that such effects exist and do exert considerable action at the level of the cell membrane of the osteoblast and osteocyte, which presumably accounts for some of the phenomena associated with bone remodeling. Based on these imaginative and careful experimental studies, at least four clinically applicable systems are now commercially available. The experimental trials suggest a high rate of success with both implanted and externally applied electrodes, and the case described by Dr Finerman is one of many that show the efficacy of the systems. The issue is no longer whether the systems exert an effect but, instead, whether that effect is optimal and, indeed, whether the cases in which they are being applied really require the use of such elaborate and expensive treatment. Unfortunately, despite the plea of some of the scientific community, neither the investigators nor the companies that control the commercial aspects of the systems seem to be able to bring themselves to do the crucial and necessary double-blind studies that would clearly establish the advantage of the systems over immobilization alone and presumably define the optimal indications for their use. Furthermore, the existing systems are probably not the final answer, but will require refinement and improved definition of the exact electrical and magnetic fields to accomplish true osteoblastic stimulation. One would hope that the work toward this end will continue,

despite the seemingly partial clinical (and total commercial) success of the available devices.

In the short time since microvascular surgical techniques were advocated for the management of soft-tissue wounds, there has been a veritable explosion of imaginative and highly useful applications of the technology, which has now become part of the armamentarium of many surgical disciplines and is applied daily in most major hospital centers to a wide variety of conditions. One of the most useful of these is that reported by Dr Meals in which living bone from one body site is transferred to another and the vascular pedicle is then anastomosed to the local arterial and venous tree. The autograft is viable and the healing occurs, not by the process of "creeping substitution" but by fracture repair, producing a much more satisfactory system for the management of skeletal defects. The graft is more likely to heal rapidly, is more resistant to infection or problems associated with a poorly vascularized bed and will, under special circumstances, rapidly hypertrophy to restore full strength to the skeleton. By use of the iliac site described by the authors, a composite graft consisting of bone, soft tissue and skin can be introduced for defects associated with trauma.

The problems with the system are related to the length of time required for the operation (often eight or more hours), the limited supply of available donor sites (only fibula, rib and iliac bone can be used) and the occasional failures when vascular supply is reduced, which leaves a patient with a less-than-satisfactory autograft implant. The future promise of this technique is great, since it may be possible when—editorial license allows me to say "when" rather than "if"—the problems of transplantation immunology are solved, to introduce allograft segments harvested from a cadaveric source that include not only the bone but the adjacent cartilaginous surface and, in the special circumstance of a growing child, the epiphyseal plate. Clearly, this is an objective that not only boggles the mind, but moistens the lacrimal ducts!

The most important advance of the past two decades in the worlds of orthopedics and rheumatology has been the introduction by Sir John Charnley in 1962 of the first successful model of the total hip replacement. Although numerous technical advances have been introduced since, the basic design remains the same and in fact has stood up well over the two decades, with countless patients now restored to excellent function and a full life because of this ingenious procedure. The complications described by Dr Moreland do not detract from the basic high-quality performance of the device but, nevertheless, represent areas which have been the subject of intensive investigation over the past several years. The use of better designed components and materials, improved cementation, prophylactic antibiotics, rigidly controlled operating room environment and drug or radiation therapy control of ectopic ossification has reduced the complications of stem breakage, aseptic loosening, infection and heterotopic bone formation to an acceptable minimum, although clearly work continues to reduce them further and will presumably be successful. As rather gently suggested by Dr Moreland (and, alas, testified to by a large number of sufferers), however, the devices used for other joints are less advanced in terms of design and elimination of problems. The devices for knees are becoming better, particularly with improved component design, better cementation and metal-backed components, but the devices currently available for implantation in the shoulders, elbows and ankles are, for the most part, rudimentary and fraught with major problems. They will in time be solved, but further work must be done to meet the standard set by the remarkable success of the hip replacement.

One of the more promising and exciting advances described by Dr Kim is the current research in porous devices that allow bony ingrowth. There is little doubt that the currently utilized system of methyl methacrylate cement has some inherent problems at the bone-cement interface, which cannot be overcome by mechanical or biological manipulation. The recent demonstration that bone will grow into appropriately sized pores in the metallic device is an exciting one, since it will provide a system that will lock in place and, theoretically at least, diminish stress shielding and other mechanical and biologic problems associated with the composite implants. These devices, like the surface replacements—both fairly radical departures from the original Charnley system—will have to be evaluated after more extensive trials and the test of time.

And now to the pursuit of the "Holy Grail" . . . is Dr Urist a true Galahad or merely a Lancelot? For most of his illustrious career in orthopedic research, Dr Urist has doggedly pursued the identification and isolation of the true "elixir of bone life," the material by which bone formation is induced at the site of fracture or injury, which ensures that we will heal bone with bone rather than with scar. As he points out, unlike other tissue sites, it is this one not-so-simple act that allows us to maintain skeletal continuity despite injury and is presumably responsible, along with other factors (see the discussion of electric fields above) for bone remodeling and turnover. As simple as the concept of an induction factor(s) sounds, it is clear that it has not been an uncomplicated route; in fact, the discussion that ends the UCLA report is a masterful review of an extensive series of experimental approaches to a most complicated problem. There is little doubt on the basis of the published work that some of the factors have now been identified and partially purified and that orthopedics is indebted to Dr Urist for his ingenious study of the elusive material. If the purification proceeds, if the cofactors can be identified and controlled, if the material can be further identified and synthesized, either chemically or by genetic engineering techniques, we are poised on the threshold of great control over the body's skeletal renewal processes. To be able to intro-

duce a readily available polypeptide to get fractures to heal, induce osteoporotic bone to become normal and grafts to unite, and so forth, is "the stuff that dreams are made of."

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Generic Medicine and Surgery in Patient Care

INCREASING ATTENTION is being given to finding ways to reduce the cost of patient care without significantly impairing its quality. Two items in this issue address different aspects of this important problem. White and co-workers document substantial differences among "low-charge," "medium-charge" and "high-charge" physicians. The high-charge physicians averaged $164 per visit, the medium-charge physicians $124 and the low-charge averaged only $97 per visit. These were clinic visits of patients who had specific chronic medical problems. They found that the high-charge physicians ordered a little more of every item or service, and sometimes a more expensive rather than a less expensive medication or laboratory test. There seemed to be no difference in the quality of the patient care outcomes. Then, in the Correspondence section, Scott notes that the "humble 5¢ generic pill compared with the 30¢ brand is ample proof that cost has nothing to do with performance," and observes that "a $10,000 hysterectomy in an elite suburban hospital is not necessarily better than a $2,000 hysterectomy in a humble city hospital." He proposes that we can and must offer *generic medicine* and *surgery* that should not affect the quality of care.

This would seem to be a concept worth further study and perhaps some experimentation. One can envision arrangements where generic patient care, consistent with quality but without the frills, could be available at lower cost, with options for the frills available for those who wanted them enough to pay the additional cost. So far this concept has been applied only to generic drugs, but why not in similar fashion recognize a basic level of medical and surgical care that is consistent with quality but devoid of unnecessary extras and therefore deliverable at less cost? Competition and the health care marketplace could then develop and offer the extras and frills for those who wanted them enough to pay extra for them. Third party payors would presumably be responsible only for generic patient care. Is this by any chance an idea whose time is about to come?

MSMW

Case Reports

Hypocalcemia Complicating Bicarbonate Therapy for Salicylate Poisoning

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SALICYLATES are an important cause of both accidental poisoning in children and suicidal overdoses in adults. Sodium bicarbonate ($NaHCO_3$) therapy has been widely recommended in the literature. A recognized but infrequently mentioned complication of alkali therapy is a reduction of ionized calcium.[1] The following case illustrates the development of symptomatic hypocalcemia with a low total serum calcium level during treatment of salicylate ingestion.

Report of a Case

The patient, a 14-year-old boy, ingested approximately 30 325-mg aspirin tablets. He began vomiting, had headache, tinnitus, orthostatic dizziness and symptomatic tachypnea, and arrived at the emergency room about six hours after ingestion. No other medications were taken. The patient had no prior history of drug overdose, was taking no maintenance medication and did not smoke or drink alcohol. Past medical history was unremarkable, with no evidence of growth disturbance, malabsorption or endocrinopathy.

On physical examination he was well developed and afebrile with a pulse rate of 100, respirations 28, blood pressure 120/80 mm of mercury and weight about 50 kg (110 lb). The patient was tachypneic with no neurologic abnormalities. There was no clinical evidence of pancreatitis or bone abnormality. Ipecac syrup was given with resultant emesis, followed by the administration of activated charcoal and cathartics.

Emergency room laboratory studies gave the following values: arterial pH of 7.44; oxygen partial pressure (tension; Po_2), 95 mm of mercury; carbon dioxide partial pressure (tension; Pco_2), 26 mm of mercury; bicarbonate (HCO_3), 18 mEq per liter (normal, 28 ± 4), and salicylate concentration, 60 mg per dl. Sodium bicarbonate, 50 mEq, was administered intravenously and a regimen of 5% dextrose in water with 100 mEq per liter of $NaHCO_3$ was begun at 100 ml an hour. Admission laboratory studies of specimens drawn about an hour after initiation of $NaHCO_3$ therapy gave the following values: serum calcium, 8.7 mg per dl (normal, 9.5 ± 1); phosphorus, 5.2 mg per dl (normal, 4 ± 1.5); sodium, 141 mEq per liter (normal, 140 ± 5); potassium 3.7 mEq per liter (normal, 3.5 to 5.0); chloride, 107 mEq per liter (normal, 100 ± 5); alkaline phosphatase, 309 IU per liter (normal, 30 to 300); albumin, 4.8 grams per dl- (normal, 4.4 ± 0.9), and total protein, 7.0 grams per dl (normal, 7.0 ± 1). Glucose was 141 mg per dl (normal, 90 ± 15) and creatinine, 1.1 mg per dl (normal, 1.1 ± 0.5). Other laboratory studies showed no abnormalities. The serum salicylate concentration 2½ hours after admission declined to 48 mg per dl.

About nine hours after admission, the patient began having numbness and paresthesias of his face and extremities with pain in his extremities. He was afebrile and normotensive with a pulse of 100 per minute and respirations 24. He was alert, oriented and hyperpneic. Hypertonus, hyporeflexia, Chvostek's and Trousseau's signs were noted. The arterial pH was 7.52; Po_2, 88 mm of mercury; Pco_2, 29 mm of mercury, and HCO_3, 28 mEq per liter. Total serum calcium was 6.4 mg per dl; magnesium, 1.3 mg per dl (normal, 2.1 ± 0.3), and potassium, 3.1 mEq per liter. Phosphate and total protein levels were not rechecked; serum hormone levels and urinary electrolytes were not measured. An electrocardiogram (ECG) showed a rate of 88 with a very prominent U wave. Intravenous administration of HCO_3 was discontinued and the patient was given 200 mg of calcium as calcium gluconate intravenously over the next hour. The calcium therapy was continued over the ensuing five hours at 100 mg an hour. Potassium chloride replacement was also given intravenously, and magnesium sulfate was administered intramuscularly. Calcium and potassium were later administered by mouth.

The patient had considerable clinical improvement after initiation of therapy. Serial serum calcium levels rose, reaching 7.3 mg per dl at 1 hour, 8.5 mg per dl at 2 hours and 8.7 mg per dl at 11 hours after initiation of infusion. The serum potassium level corrected to 4.6 mEq per liter and the magnesium level to 2.0 mg per dl. The prominent U waves disappeared from the ECG tracing with correction of the electrolyte abnormalities. The patient continued to do well with no suggestion of underlying illness during the rest of his hospital stay. Discharge occurred on the fourth hospital day, 36 hours after discontinuation of calcium supplementation, with a serum calcium value of 8.7 mg per dl. The patient failed to keep follow-up appointments.

Comment

The recommended treatment of salicylate intoxication includes hydration with administration of potas-

(Fox GN: Hypocalcemia complicating bicarbonate therapy for salicylate poisoning. West J Med 1984 Jul; 141:108-109)

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
HCO_3 = bicarbonate
$NaHCO_3$ = sodium bicarbonate
Pco_2 = carbon dioxide partial pressure (tension)
Po_2 = oxygen partial pressure (tension)

sium chloride and sodium bicarbonate until the salicylate level is therapeutic.[2] Recommendations for HCO_3 include initial administration of 88 mEq (two ampules) over the first one to two hours, followed by a maintenance solution containing 20 to 88 mEq per liter of HCO_3, depending on hydration state and the serum potassium level. An initial urine flow rate of 10 to 15 ml per kg of body weight per hour is recommended, followed by 3 to 6 ml per kg per hour. (Initial and maintenance solutions may need to be altered depending on the patient's serum and urine pH and urinary output.) Treatment of our patient fell within these guidelines; less than three ampules of $NaHCO_3$ had been infused by the time symptoms developed.

Reviews on the pathophysiology and treatment of salicylate toxicity occasionally mention tetany during the alkalotic phases of the condition.[3] Tetany has been presumed to be due to a diminution in ionized calcium, without necessarily altering measured total serum calcium. It has been stated that tetany is rarely severe unfewer than three ampules of $NaHCO_3$ had been infused amounts. Our case suggests that tetany may occur with the usual recommended HCO_3 doses for salicylate poisoning. Although it is possible the patient's tetany was due to alkalosis from his salicylate poisoning, his initial laboratory values suggest that this was not the case. The first salicylate concentration was in the range of mild toxicity, and subsequent levels declined. The initial arterial pH was 7.44, and a simultaneously drawn calcium level was normal, indicating that alkalosis during the prehospital phase of the overdose was not a contributing factor. Only after initiation of medical therapy did hypocalcemia become evident; discontinuing the $NaHCO_3$ therapy and administering calcium rapidly reversed the patient's symptoms.

We can only speculate about the pathogenesis of hypocalcemia in this patient. The first serum calcium level of a specimen drawn after administration of about 60 mEq of sodium bicarbonate was in the low-normal range. The possibility of inapparent underlying illness exists, though the patient's history and physical examination were compatible with that of an otherwise normal teenager. Alkaline phosphatase and phosphate levels were normal for age.

Alterations in hormonal control of serum calcium could be postulated; serum parathyroid hormone and calcitonin levels were not measured. Moderate hypomagnesemia was recorded in our patient, and it is known that profound hypomagnesemia interferes with parathyroid hormone secretion in vivo.[4]

A renal mechanism is also plausible, considering that kidneys filter 5,000 to 8,500 mg of calcium a day, with 90% to 95% of filtered calcium being resorbed by the renal tubules. A change in efficiency with which calcium is resorbed can greatly alter urinary calcium excretion and plasma calcium. Calcium complexes are not resorbed by the renal tubules, and under physiologic conditions, the acidity of tubular fluid inhibits calcium-anion interactions.[5] Therefore, administration of HCO_3 may interfere with the renal conservation of calcium.

In dogs there is a linear relationship of about 1:1 between ionized calcium clearance and sodium clearance during saline infusion, independent of urine pH. Urinary calcium loss accompanying excretion of the sodium load (as $NaHCO_3$) is also possible.[6]

Few reviews of salicylate poisoning recommend routine determination of serum calcium level during treatment. The compilers of Poisindex suggest measuring electrolytes, but no specific mention is made of calcium.[2] Hypokalemia frequently complicates salicylate overdose, and it should be noted that administration of potassium to a hypocalcemic patient can precipitate or worsen signs and symptoms of hypocalcemia.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Generic Medicine and Surgery

TO THE EDITOR: The medical community is not united about how to control the mushrooming cost of health care. Many of us are not even convinced that cost control is justified in this uniquely successful American accomplishment. There is almost uniform resentment of an outside intrusion. So far all efforts to control the cost of health care have failed (as the editorial "Health Care and Not Enough Dollars"[1] notes). I believe in laissez-faire. But now the taxpayers are revolting and some patients avoid medical help because they cannot afford it. It is time to face up to our economic difficulties.

The explosion of health care costs started in earnest after the direct government involvement in the 1960s. It has created a giant appetite for the economic pie stuffed with federal dollars. It has also created the biggest and most expensive medical bureaucracy ever and this continues to grow.

The cost of health care cannot be controlled without reducing the current legal exploitation of the health industry called the "liability crisis." The legal establishment has found a veritable gold mine in the uncertain abysses of this biological science. The clout of the health establishment to control this legal development is just about nil. Similarly the abuses of the workers' compensation cannot be controlled without legislative solution. And all that is charged to the cost of health care.

The value of the much publicized competition to reduce costs is doubtful. In a community with one hospital there is no alternative. A family that is established with a physician will not abandon the trusted family doctor for an advertising gimmick. Family doctors will refer their patients to consultants proved reliable, although there is an increasing depersonalization of medicine in the big cities. Most physicians cannot transfer their own work to a cheaper hospital; staff privileges are hard to come by.

The chemical-physical technology has a scientifically glorious and economically troubled place in this process. There are too many companies in this profitable business, but we are glad to pay for prestige and medical benefit. The high technology has a specific but limited niche in most hospitals. Yet some keep ordering tests to pay for the equipment and then for profit, since these departments are the best money-makers in most institutions. If we would omit half of the tests we order today, the quality of health care would not be affected.

The pharmacological industry might be compared with the field of diagnostic technology. The humble 5¢ generic pill compared with the 30¢ brand name equivalent is ample proof that cost has nothing to do with performance. Most medical practitioners discard valuable drug samples every week. Many medical publications are financed by drug advertising dollars yet if we would discard half of the printed medical material we receive in the mail, it would have no effect on disseminating medical information. In fact if we would discard 80% of all the drugs on the market, it would have little effect on medical care, since most of them are variations of a few. This brings up the difficult question of tinkering with free enterprise. We cannot equate the frills of free enterprise with quality of medical care. A $10,000 hysterectomy in an elite suburban clinic is not necessarily better than a $2,000 hysterectomy in a humble city hospital.

The prime cause of all these problems is the medical mentality. We teach young doctors not to rely on clinical judgment or on simple tests of the past. They must prove their professional prowess by ordering the latest tests, the more the better. And thus they are reluctant to make any medical judgment without the support of several objective tests. We also practice in a wealthy free enterprise system. The more money we make the better we are. Success is measured by growth and advancement, not by thrift and conservativism. In our haste for progress we might call a conservative doctor backward, even incompetent.

We must separate the very expensive research-academic medicine from the delivery of daily routine health care. Many physicians coming from academic training continue to follow esoteric research protocols. Routine care should be simple and affordable. Finally we must mention hospitals, which we love to blame for our economic trouble. It is easy to blame an impersonal entity like a hospital which is the concentration of our economic excesses. If we trim our excesses this popular scapegoat will also be vindicated.

The current failure to control cost of health care calls for a sincere mea culpa. In spite of much pious rhetoric no hard effort is made by anyone to reduce cost. The political leadership, lacking insight into this

complex system, passes legislation that creates only confusion, augments bureaucracy and aggravates the crisis. Because of an aging population and the advancement of science, the cost of health care will be higher than other aspects of our economy. Free enterprise is very resistant to controls. The accomplishment of American medicine is the result of strife and imagination of free enterprise. We cannot touch that. But we can and must offer *generic medicine and surgery* by trimming bureaucratic and legal excesses and the frills of free enterprise and that should not affect the quality of health care.

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REFERENCE

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Pruritus of Poison Oak Dermatitis—Other Views

To the Editor: Harry Daniell's hot water treatment for the pruritus of poison oak dermatitis,[1] discussed in his April letter, will indeed mask the symptoms for several hours. It works in the same fashion as hard knocks upon the head for a headache: it makes one forget how bad the initial symptoms were. Likewise afterwards one may well need stronger medicine to effect a cure.

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REFERENCE

1. Daniell HW: Treatment for rhus dermatitis (Correspondence). West J Med 1984 Apr; 140:619-620

* * *

To the Editor: With the advent of the summer recreational season, we feel Dr Daniell's recommendation for hot showers for rhus dermatitis[1] could be deleterious. We believe most dermatologists would prefer several *tepid* showers a day to reduce symptoms of itching and burning. The mechanism by which bathing in tepid water reduces itching is unknown. It may result from the hydration of the stratum corneum and subsequent increased rate of evaporation of water from the skin surface. A tepid shower is approximately 90°F (32.3°C) or cooler. A hot shower would certainly be any temperature over 105°F (37.8°C).

While hot water may mask symptoms of itching by substituting sensations of temperature which exceed the itch/pain stimulus, bathing in hot water may actually increase the physiologic sequelae of contact dermatitis: vasodilatation, erythema, and edema. In addition, the rebound increase in skin surface water evaporation may aggravate underlying dryness in predisposed individuals such as psoriatics or patients with atopic dermatitis. Consequently, these individuals may experience paradoxical increased itching as their skin feels "drier," usually within an hour of bathing. Repeated exposure to very hot water only increases the severity of the itching. Patients must be carefully instructed in the difference between tepid water and hot water, avoiding the latter if possible.

In addition, we certainly agree that topical corticosteroids are usually inadequate therapy for moderate to severe rhus dermatitis, but we disagree with the statement that systemic steroids are not worth the risk of the side effects. Dr Daniell did not state what dosage of systemic steroids he routinely administered. In our experience, patients are too frequently administered inadequate doses to provide pharmacologic relief (20 to 30 mg of prednisone daily).

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REFERENCE

1. Daniell HW: Treatment for rhus dermatitis (Correspondence). West J Med 1984 Apr; 140:619-620

* * *

To the Editor: I feel compelled to write in order to critique some of the comments by Dr Harry Daniell, regarding the treatment of rhus dermatitis, in the April issue.[1]

Dr Daniell maintains that his hot soapless shower technique is more effective than "conventional therapy." It would have been appropriate for Dr Daniell to elucidate his list of conventional therapy so that the reader could make a comparison of his innovative therapy compared with the conventional therapy.

He also states that "most primary physicians and dermatologists, however, are unaware of its use." I doubt that he did any large survey. I'm aware of "hot bathing" as a therapeutic modality and so are other dermatologists and more than likely other primary physicians.

He states that "hot bathing is safe." I beg to differ, having seen second-degree burns on patients who were unable to discriminate the different degrees of temperature of "comfortably hot," "hot" and scalding. It is a well-known fact that the skin can accommodate to increasing degrees of water temperature if the temperature is raised slowly. Thus, I've seen a patient who started out with warm water on his feet and was able to increase the temperature to boiling simply by slowly increasing the temperature; he had no knowledge that a third-degree burn was in progress, since symptoms were not intense. In addition, those patients with a neuropathy should be extremely careful about the temperature of water upon their skin.

Most dermatologists would agree that topical steroids are useful for only the mildest cases of rhus dermatitis. However, they are rather safe and frequently are sufficient to provide some relief of symptoms.

The side effects of systemic steroids do exist; however, there are few other therapeutic modalities which even approach their effectiveness when they are properly administered. It is unfortunate that Dr Daniell finds the side effects of systemic steroids unacceptable. Having treated many patients with rhus dermatitis for more than 20 years, I am still waiting for that first case of an

unacceptable side effect when the medication is used properly in a rational and appropriate fashion.

Dr Daniell also stated that secondary infection is a "frequent complication of conventional therapy." His experiences regarding secondary infection must certainly be unique and perhaps are worth reporting in a double-blind controlled research study.

In summary, in my opinion, hot showers are not to be generally recommended to all patients with rhus dermatitis, especially due to the potential side effects of such therapy. The benefits from more conventional therapy such as systemic steroids properly utilized are worthwhile for achieving resolution of a troublesome dermatitis.

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REFERENCE

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Do-Not-Resuscitate Orders

TO THE EDITOR: Regarding the letter from medical student Marc Tunzi on do-not-resuscitate orders,[1] I am delighted that medical students have such sensitivity. Please remember, Mr Tunzi, that the house officers you so disdain for determining no-code status in such rapid fashion are trained by the staccato pace of the clinical arena where delay and indecision in evaluation of, say, respiratory failure or meningitis can lead to disaster. They know likewise that even short delay of no-code orders leads not to happy outcomes but to painful and degrading perpetuation of painful illness that is agonizing to both patients and their families.

Save a copy of your letter, Mr Tunzi, and after your next 12 long months of internship, read it again. You will realize how much you have grown and how much more complex your world has become.

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Ending Physician Maldistribution

TO THE EDITOR: I wish I could be as positive as Crowder and associates[1] over the results of the California AHEC program. Nowhere does the "Program Results" section report on how many health professionals have actually settled in the medically underserved portions of the state. I propose a different system to end physician maldistribution.

We seem to have a physician glut and a coexisting and paradoxical physician shortage. One cause of this phenomenon could well be the large debt that a young physician accumulates during medical training. It is an economic fact that it is easier to pay off this debt when you practice in a large population center.

The costs of office equipment and supplies are the same whether a physician practices in a small community or a large one. Rents and office help cost only a little less in a small town—not enough to make up for lower income and a slower debt reduction. It is surely recognized by all young interns that a neurologist or an orthopedist or even a pediatrician will have fewer cases and less income in a small, rural catchment area. A physician's time is less effectively utilized when he or she travels to four or five hospitals, 50 miles from one another, to see one patient in each hospital. The unproductive travel time lowers his or her income even further. What would be the incentive, therefore, to practice in a small-income, rural area, watching his or her debt diminish ever so slowly every year?

My suggestion to narrow this debt/rural practice gap is to forgive medical school debts in exchange for a contract to practice within a rural county or low-population area for a specified number of years. If we can develop a financial instrument whereby an association of rural counties or even a small-population state would pay off medical education-related debts in return for a multi-year contract, we could perhaps get a lot of young doctors with up-to-date medical education practicing in the outlying areas not only for the duration of their contract periods but also afterwards because they had become used to the pleasures of a low-pressure life in a small community. Hunting, fishing, horse-breeding all come easier in the country and many physicians, as other people, enjoy this life. This could be the method to have country pleasures—and provide good care to small-town populations.

As it is now, we are trying to catch our tails: we produce more physicians just to see them settling in Los Angeles, for example (and hoping to "graduate" eventually to Beverly Hills), and the original goal of producing physicians to end the physician shortage in the rural areas keeps eluding us. The financial tool could be the ending of capitation grants to medical schools and using the same money for debt reduction by giving it to rural county plans. Of course, we may forgive the debts of young graduates who would have located in underserved, rural counties anyway (although there can't be many, based on currently known preferences) but if there were a perfect system of putting out our money with 100% efficiency, we, and especially the federal government, have yet to find it.

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Topics in Primary Care Medicine

Systemic Effects of Oral Contraceptives

THOMAS M. KELLY, MD, *Salt Lake City*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The percentage of American women choosing an oral contraceptive agent as their method of birth control decreased during the late 1970s following the publication of reports about side effects of these agents, especially reports of an increased incidence of cardiovascular disease among oral contraceptive users. Many such studies, however, were based on the early years of oral contraceptive use, when the drugs contained much higher doses of estrogen than they do now. Reduced estrogen content has significantly decreased the risks of oral contraceptive use. Nevertheless, the systemic effects of oral contraceptive drugs still need to be kept in mind by primary care physicians.

Hepatic Effects

While sex steroids secreted by the ovary drain into the systemic venous system, the estrogen and progestin of combination oral contraceptives enter the portal circulation first. Consequently, to achieve effective hormone levels in nonhepatic target tissues, the liver must be exposed to high sex-steroid concentrations.

Binding Proteins

Estrogens stimulate hepatic production of several protein groups. Levels of the hormone-binding globulins for thyroxine, cortisol and sex steroids rise (Table 1). The rise causes a transient fall in free hormone levels that, through normal functioning feedback loops, causes increased secretion of stimulating hormones by the pituitary. Hormone production by target glands then increases, restoring the concentrations of free hormones and raising total hormone concentrations. Physicians need only be aware of a patient's use of oral contraceptives to correctly interpret measurements of total hormone levels and so avoid unnecessary diagnostic or therapeutic maneuvers.

Coagulation

Hepatic production of coagulation factors is also increased by the estrogen in oral contraceptive agents. Levels of factors II (prothrombin), VII and X are elevated in the plasma of women taking oral contraceptives compared with levels in control subjects. Some investigators have found the concentration of factors I (fibrinogen), V, VIII, IX and XII to be increased as well. Because clotting factors are normally present in amounts greater than necessary for adequate hemostasis, it is unclear if the increases induced by oral contraceptive drugs are physiologically significant. The coagulation tests commonly done, such as the prothrombin and partial thromboplastin times, are generally unaffected by oral contraceptive use. No consistent changes attributable to the use of these drugs have been found in the fibrinolytic system or in platelet adhesiveness, whereas several studies have shown small platelet count increases of doubtful clinical significance.

Glucose Homeostasis

Combination oral contraceptive drugs impair glucose tolerance, an effect proportional to their estrogen content. Because parenteral administration of natural estrogens reduces hyperglycemia in patients with diabetes, the diabetogenic effect of oral contraceptives probably results not from their inherent estrogenic activity but rather from an action specific to their synthetic estrogens or from their route of administration. Estrogen-mediated inhibition of cortisol metabolism and elevation of plasma cortisol levels may contribute to the impairment of glucose tolerance by oral contraceptives.

By whatever mechanism, the use of oral contraceptives produces a state of insulin resistance. Women whose insulin secretion increases will have effective compensation, whereas in those whose pancreatic re-

(Kelly TM: Systemic effects of oral contraceptives [Topics in Primary Care Medicine]. West J Med 1984 Jul; 141:113-116)

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ABBREVIATIONS USED IN TEXT
HDL=high-density lipoprotein
LDL=low-density lipoprotein
VLDL=very-low-density lipoprotein

serve is limited by obesity, advanced age or hereditary factors, glucose intolerance of a severity proportional to their pancreatic deficiency develops. Therefore, women at high risk for the development of diabetes, those who are older than 35, are obese, have a strong family history or who have had glucose intolerance during previous pregnancies should be either not given combination oral contraceptives, given them only with close monitoring or treated with progestin-only pills that appear not to affect glucose tolerance.

Lipid Metabolism

Taking oral contraceptive drugs raises plasma triglyceride levels 30 to 50 mg per dl in users of all ages. The associated increase in very-low-density-lipoprotein (VLDL) concentrations produces a type IV hyperlipoproteinemia pattern. Available evidence suggests that elevated VLDL concentrations result from increased hepatic production, possibly mediated by hyperinsulinemia, and from decreased peripheral clearance due to reduced lipoprotein lipase activity. Oral contraceptives have also been reported to cause massive hypertriglyceridemia and consequent pancreatitis in a few women with underlying, often unrecognized, hyperlipoproteinemia.

Oral contraceptives have a less striking effect on plasma cholesterol, raising its concentration only slightly, if at all. More important, however, are the effects of these drugs on the distribution of cholesterol among lipoprotein fractions. Oral contraceptive use is associated with higher levels of low-density-lipoprotein (LDL) and VLDL cholesterol, especially in women younger than 30. These changes, unfavorable with respect to the risk of coronary artery disease, contrast with the favorable effects of estrogens alone and thus may be due to the progestin component of oral contraceptive drugs or to the interaction of the two steroid types. Oral contraceptive effects on high-density-lipoprotein (HDL) cholesterol are closely tied to the amount of estrogen in a given preparation. High-dose (more than 50 μg) estrogen agents increased HDL cholesterol levels, whereas the low-dose preparations more commonly used at present produce no significant change. Because of the effects of oral contraceptives on plasma lipids, it seems clinically prudent to measure cholesterol and triglyceride levels in women before and while they are taking contraceptive drugs and to consider hyperlipidemia a relative contraindication to their use.

Hepatic Adenomas

The nonmetabolic effects of oral contraceptive use on the liver include an association with a variety of hepatic vascular disorders such as thrombosis of the large hepatic veins (the Budd-Chiari syndrome), occlusion of small hepatic veins and periportal sinusoidal dilatation. Oral contraceptive intake also increases the risk for hepatocellular adenomas, histologically benign tumors that can be fatal because of a propensity to bleed. Depending on the occurrence of hemorrhage and its severity, hepatic adenomas can present with a right upper quadrant mass; sudden, severe, subcostal pain, or shock. Epidemiologists concur that the risk of hepatic adenoma rises with the duration of oral contraceptive use, but they fail to agree on which component is responsible for the association. The history and physical examination are presently the only practical screening methods, as the presence of hepatic adenomas does not alter the serum levels of liver enzymes. Most adenomas diagnosed before hemorrhage and not operated on have regressed with discontinuation of the contraceptive regimen.

Biliary Dysfunction

Oral contraceptive use can produce cholestatic jaundice and often does so in women with a history of pruritus or jaundice during pregnancy. Such women appear to be genetically predisposed to sex steroid-induced cholestasis. The synthetic estrogens in contraceptive drugs also reduce bile flow. The resultant biliary stasis predisposes to gallstone formation and may account for the increased incidence of oral contraceptive-associated cholecystitis and cholelithiasis noted in some but not all studies.

Cardiovascular Effects

The most significant adverse effects of oral contraceptive use may be those involving the arterial and venous vascular systems. Despite considerable controversy about these effects, several reliable conclusions can be drawn.

TABLE 1.—*Changes in Laboratory Test Results Caused by Oral Contraceptives*

Increase in Total Hormone Concentrations (and Hormone-Binding Globulins)
Thyroxine (thyroid-binding globulin)
Cortisol (transcortin)
Sex steroids (sex steroid-binding globulin)
Growth hormone
Prolactin
Aldosterone (due to elevations of angiotensinogen and plasma renin activity)
Effects on Coagulation Variables
Increased plasma fibrinogen and prothrombin
Increased clotting factors VII, X (and possibly V, VIII, IX and XII)
Increased platelet count
Metabolic Alterations
Abnormal glucose tolerance with increased serum insulin
Increased plasma triglycerides
Increased free fatty acids
Shift in distribution of cholesterol among lipoprotein fractions
Miscellaneous (Effects Generally Small)
Decreased serum albumin
Increased serum amylase
Elevation of erythrocyte sedimentation rate
Decreased haptoglobin
Increased iron-binding capacity (increased transferrin)
Increased serum transaminases and γ-glutamyl transpeptidase
Decreased vitamin B_{12} and folate

Hypertension

First, the combination oral contraceptive drugs appear to raise the blood pressure of nearly all women who take them, an effect seen anywhere from ten weeks to two years after initiation of their use. The increment in blood pressure is generally small and in only 1% to 15% of oral contraceptive users does a blood pressure of greater than 140/90 mm of mercury develop. Women who have had hypertension during a previous pregnancy have the greatest hypertensive response to oral contraceptive drugs. For all women, the systolic blood pressure increases an average of 10 to 15 mm of mercury, whereas the diastolic blood pressure rises 5 to 10 mm of mercury.

The consistent finding of a greater change in systolic than in diastolic blood pressure suggests that the primary hypertensive effect of oral contraceptives is on blood volume and cardiac output and therefore mediated by the ability of estrogens to cause salt and water retention. Estrogens in oral contraceptives may also produce hypertension through the renin-angiotensin system because they raise the level of angiotensinogen, the substrate of renin. On the other hand, when the amount of estrogen is held constant, the incidence of hypertension increases with the dose of progestin, indicating a hypertensive role for that component also.

Women taking oral contraceptives should have their blood pressure checked whenever they are seen clinically and, if it is found elevated, should be switched to a lower dose estrogen preparation or taken off the drug regimen. The hypertensive effect of oral contraceptives appears to be reversible.

Cerebrovascular Disease

During the late 1960s, British studies of reproductive age women with cerebrovascular disease showed that there were more oral contraceptive users among cases than would have been predicted from the frequency of the use of oral contraceptives among controls. The differences found were statistically significant despite the small number of cases. A subsequent cooperative study done in the United States confirmed an association of thrombotic and hemorrhagic stroke with current oral contraceptive use and found the relative risk of cerebral ischemia or thrombosis to be about nine times greater in oral contraceptive users than in nonusers.

Both the dose of estrogen and the dose of progestin have been found in different studies to correlate with the risk of stroke. Because early investigators found a decreasing risk of cerebral thrombosis with a decrease in estrogen content from 150 to 100 to 50 μg, a further reduction in the incidence of cerebrovascular disease would be expected for users of the more recently marketed 30-μg estrogen preparations. One study has in fact shown such a reduction in stroke occurrence. In contrast, data from Sweden showed no change in reported cerebral thromboembolic disease accompanying the nationwide shift to low-dose-estrogen oral contraceptives.

TABLE 2.—*Age-Adjusted Relative Risk of Myocardial Infarction as Influenced by Use of Oral Contraceptives and Cigarettes**

Cigarette Use†	*Oral Contraceptive Use*‡	
	No	*Yes*
No	1.0§	4.5
Yes	7.0	39.0

*From Shapiro et al.
†Defined as 25 or more cigarettes smoked per day.
‡Defined as use within the month preceding hospital admission for myocardial infarction.
§Risk of myocardial infarction in this group taken to be the reference standard and set equal to unity.

Disparity in study results is most striking with regard to oral contraceptive use and subarachnoid hemorrhage. Two large epidemiologic surveys found a pronounced increase in cases of subarachnoid hemorrhage among oral contraceptive users whereas two equally thorough investigations failed to detect such an association. These discrepancies probably stem from different methods of case finding and from unappreciated differences in the studied populations. The thrust of the reported data indicates that if oral contraceptives are not used by women who are older than 35 years, who smoke or who are hypertensive, then the risk of subarachnoid hemorrhage or any other cerebrovascular complication is indeed quite small.

Myocardial Infarction

Although their effects on blood lipids, carbohydrate tolerance and blood pressure made oral contraceptives suspect for predisposing users to ischemic heart disease, myocardial infarction was the last of the major thromboembolic disorders to be associated with their use. Even now that their use has been shown to increase the risk for myocardial infarction, many aspects of that relationship remain controversial. The relative risk of myocardial infarction in oral contraceptive users has been anywhere from zero to sixfold greater than in nonusers. Such diversity of results appears related to the confounding effect of other myocardial infarction risk factors, especially cigarette use and age. The effects of smoking and oral contraceptive use seem to be synergistic rather than simply additive (Table 2). With regard to age, the correlation between oral contraceptive use and the incidence of myocardial infarction is not statistically significant for women younger than 30 to 35 years of age.

Despite earlier studies showing a correlation between estrogen dose and the risk of coronary thrombosis, disparate results have been obtained as to whether deaths due to ischemic heart disease have decreased with the decrease in estrogen content of oral contraceptives from 50 to 30 μg. Whether there is a residual effect of past oral contraceptive use on myocardial infarction risk and whether the risk of ischemic heart disease increases with the duration of oral contraceptive use are also unresolved questions.

Venous Thrombosis

In contrast to the controversial relationship between oral contraceptives and arterial occlusive disease, the

data regarding the effect of their use on venous thrombosis are quite straightforward. Surveys done in the late 1960s showed that the risk of death from pulmonary embolism among oral contraceptive users was seven to eight times greater than that in nonusers, and the incidence of hospital admission for pulmonary embolism and deep venous thrombosis was ninefold to tenfold higher. Furthermore, a correlation was found between the dose of estrogen and the risk of deep venous thrombosis and pulmonary embolism, a finding possibly explained by the previously outlined effects of estrogen on coagulation factor levels. The results of such studies provided the major impetus for the introduction of oral contraceptive drugs with lowered estrogen content. The reduction in estrogen dose has been followed by a decrease in the risk of deep venous thrombosis and superficial thrombophlebitis and a reduction in the number of deaths attributable to venous disease in oral contraceptive users.

Effects on Malignant Disorders

While much attention has been focused on the cardiovascular effects of oral contraceptive drug use, many patients and physicians are concerned about the possibility of these drugs inducing tumors in sex hormone-sensitive tissues. Anxiety is engendered because treatment of postmenopausal women with unopposed estrogen has increased the prevalence of endometrial carcinoma and because the estrogen dose in oral contraceptives is more potent than that usually used during menopause.

However, the preponderance of available evidence, including recently reported data from the Multicenter Cancer and Steroid Hormone Study, coordinated by the Centers for Disease Control, indicates that oral contraceptive use for ten years or longer does not increase the risk of breast cancer. This is true even in women who, because of a history of benign breast disease or a family history of breast cancer, might be considered most sensitive to a tumor-inducing effect. On the contrary, there are data showing that taking oral contraceptives reduces the risk of fibrocystic breast disease, with the degree of reduction related to the duration of use. With respect to ovarian and endometrial cancers, the evidence fails to support a tumorigenic effect of the drugs. In fact, they may protect users from the development of a malignant lesion. The beneficial effect of oral contraceptives on ovarian cancer incidence may be due to their suppression of gonadotropins and ovulation. The positive effect on uterine carcinoma risk is probably due to the estrogen-opposing action of the progestin in combination oral contraceptives. The recent trend to reduce the estrogen content of oral contraceptives and depend more on the progestin to inhibit fertility may further decrease the risk of endometrial cancer in users.

Other Effects

Headache

In as many as 3% to 5% of women who take oral contraceptives, a headache syndrome, especially migraine, develops or is exacerbated. The cause of such headaches and their relationship, if any, to cerebrovascular thromboembolic disease are uncertain.

Beneficial Gynecologic Effects

Because the progestin in combination oral contraceptives prevents heavy and prolonged menses, the risk of iron deficiency anemia is reduced among users. By inhibiting ovulation, oral contraceptives decrease the incidence of the premenstrual syndrome. In addition, they lower the risk of pelvic inflammatory disease, especially gonococcal, and as a result also reduce the incidence of ectopic pregnancies.

Drug Interactions

Modification of drug activity by oral contraceptives can be predicted from the effects already outlined. Oral contraceptive-induced sodium retention, impaired glucose tolerance and increased clotting factor levels may necessitate increased doses of antihypertensive, hypoglycemic and anticoagulant agents. Because the hemostasis-altering effects are due to the estrogen content, such problems may also be managed by using low-estrogen or progestin-only preparations or nonhormonal methods of contraception.

Several commonly used medications impair the action of oral contraceptives. Sedative, hypnotic, anticonvulsant and nonsteroidal anti-inflammatory agents all can increase hepatic microsomal enzyme formation, leading to more rapid breakdown of the estrogen and impairment of the contraceptive effect. Antibiotics, including penicillin, which alter bowel flora and thereby reduce sex-steroid absorption and the enterohepatic circulation of estrogens, may also interfere with the action of oral contraceptives.

Conclusion

Many side effects of oral contraceptives were not reported until after their marketing and widespread use. The cataloguing of complications characterized the first period of clinical reports on the use of these drugs. More recently has come documentation of the beneficial health effects of oral contraceptive use and the positive impact of reducing their estrogen content. The future should provide us with answers regarding what long-term effects, if any, these drugs may have. Since their introduction, they have always been the most effective method of temporary fertility control; now they are proving to be very safe agents as well.

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Ordering Decision and Clinic Cost Variation Among Resident Physicians

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Physicians vary considerably in the services they order for their patients. We examined ordering variation among 47 resident physicians during 4,991 continuity clinic visits with patients who had specific, chronic medical problems. We ranked the physicians by their average charge per visit and grouped them into three equal categories. High-charge physicians averaged $164 per visit, medium-charge $124 and low-charge $97. In comparing the frequencies with which physicians in each group ordered a wide array of specific laboratory tests, x-ray studies, medications and miscellaneous items, we found that ordering variation among the physician groups was not confined to certain decisions or categories of services. High-charge physicians ordered a little more of nearly every item or service. Although the magnitude of ordering variation for each item was small, the sum over many items was great, suggesting that cost-containment efforts may have to focus on the "little ticket" decision-making style of expensive physicians.

(White RE, Skipper BJ, Applegate WB, et al: Ordering decision and clinic cost variation among resident physicians [Costs of Care]. West J Med 1984 Jul; 141:117-122)

An important issue of the cost of medical care is what services physicians order for their patients because these ordering decisions determine 50% to 80% of all medical care expenditures,[1] include the ordering of unnecessary services[2,3] and vary from physician to physician. Substantial physician variation has been described in outpatient care among health maintenance organization physicians,[4,5] private internists,[6,7] academic internists[8,9] and resident physicians.[10] Physicians differ in ordering laboratory tests,[4-9,11] x-rays,[4,5,7,11] medications[7,8,11,12] and consultations[7] and in requesting return visits.[4,7] Previous investigators have described the variation primarily by reporting summary figures—that is, number of tests per visit or average charge per visit—which has left obscure the exact source of the variation. Do some physicians order more of all items, just certain items or more expensive ones and are their ordering habits consistent across diagnoses and categories of services—that is, laboratory tests, x-ray studies, medications and the like?

Perhaps the source of physician variation can be explained by borrowing the "little ticket" hypothesis offered by Moloney and Rogers[13] to explain the cost escalation of health care. They suggested that ordering of the "big ticket" technologies (such as computed tomographic scans) is less costly than the cumulative effect of ordering "thousands of [the] small tests and procedures" that are more frequently used by physicians and that individually cost little. Our study was controlled for diagnosis and we scrutinized physician ordering decisions to evaluate the plausibility of applying the "little-ticket" hypothesis to physician ordering and cost variation.

Methods

The study was conducted in the General Internal Medicine Clinic at the University of New Mexico/

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Bernalillo County Medical Center (Albuquerque). Internal medicine residents attend the clinic a half-day each week and provide continuity of care to patients who have chronic medical disorders. Clinic patients are assigned to resident physicians on a nonselective, first-available-appointment basis and continue to be seen by that physician for the duration of the physician's residency. Data from 4,991 clinic visits between 1,284 patients and 47 resident physicians were obtained in a uniform, prospective manner between October 1978 and April 1980. About 51% of these visits occurred between October 1978 and August 1979; the rest occurred during a cost-containment, educational program carried out in the clinic from August 1979 through April 1980.[14] Data were collected only from visits with patients who had common, chronic disorders: hypertension, congestive heart failure, diabetes mellitus or degenerative joint disease. Visits with new patients—that is, the first two visits—were excluded because extra charges would presumably be associated with the initial clinic evaluation.

Recorded data included visit date, patient and resident identification, patient age, resident year, payment or insurance coverage status, the return appointment interval prescribed by the physician, study diagnosis(es), study diagnosis severity, the number of nonstudy diagnoses and all physician orders. Each item or service ordered was assigned a charge based on the 1978 University of New Mexico (UNM) Hospital list of charges, which was held constant throughout the study. The charges were categorized (clinic visit fee, laboratory charges, radiology charges, medication charges and miscellaneous charges for items such as consultations, electrocardiograms or physical therapy) and totalled. Whenever a consultation was ordered, a fixed amount of $160 was charged to the physician because that was the average first visit charge incurred in 50 consecutive referrals from Internal Medicine Clinic to various specialty clinics. Subsequent specialty clinic charges were excluded. The drug charges for a visit were the charges for the first prescription filled and the expected charges for all prescribed refills until the next appointment ordered by that resident. These methods of assigning consultation and future drug charges to a visit were felt to best reflect the monetary consequences of a physician's ordering decisions for that visit. Additional details about these methods may be found elsewhere.[15]

Patient charges were presumably determined partly by factors that resident physicians could not influence, especially illness complexity. Our most important control of illness complexity was by examining only clinic visits selected by prospectively established criteria, thereby making all patients more uniform. Additional control over illness complexity was retrospectively accomplished before examining actual physician ordering decisions. This control involved adjusting total visit charges to reduce the influence of seven variables (henceforth called covariates): four covariates—study diagnoses or combination thereof, severity rating, number of nonstudy diagnoses and patient age—measured illness complexity and three covariates—resident year, payment or insurance status and whether or not the visit took place before or during the cost-containment educational program—measured other factors study physicians could not influence. (During the intervention a 5% reduction in the average clinic charge was accomplished and is the subject of another detailed article.[15]) The adjustment was made on each one of the 4,991 visits with analysis of covariance. With this method, each total visit charge was adjusted up or down by the influence of each covariate, thereby furthering efforts to make all patients more similar. Combined, the seven covariates accounted for 6.3% (analysis of covariance, $R^2 = .063$) of the charge variation among all clinic visits.

Using adjusted total charges, a mean adjusted charge

TABLE 1.—*Average Charges and Average Physician Ordering Frequencies per Clinic Visit*

Clinic Patient Care	*Resident Physician Charge Category*			*Cost Differences Between Low- and High-Charge Physicians*
	Low	*Medium*	*High*	
Resident physician, No.	16	15	16	
Total clinic patient visits, No.	1,862	1,449	1,680	
Visit fee: Average charge per visit ($)	14.00	14.00	14.00	00.00
Laboratory tests: Average charge per visit ($)	13.58	16.05	24.29	10.71
Visits in which lab tests were ordered (%)	42	50	57	
Average number of tests ordered	2.35	2.43	3.06	
Average charge per test ($)	12.82	13.58	14.31	
X-ray studies: Average charge per visit ($)	3.88	5.95	6.96	3.08
Visits in which x-ray studies ordered (%)	7	12	12	
Average number of x-rays ordered	1.12	1.18	1.28	
Average charge per x-ray ($)	41.19	43.65	46.35	
Drugs: Average charge per visit ($)	48.23	63.89	93.97	45.74
Visits in which drugs were ordered (%)	89	91	91	
Average number of drugs ordered	3.21	3.53	4.01	
Average charge per drug ($)	16.82	20.09	26.04	
Miscellaneous: Average charge per visit ($)	16.83	23.62	24.82	7.99
Visits in which any consultations were ordered (%)	7	11	11	
Visits with more than one consultation (%)	0.5	0.6	1.2	
Total of average charges per visit ($)	96.52	123.51	164.04	67.52
Range	72 to 106	108 to 134	134 to 250	

per visit for each resident was calculated, and residents were then sequentially ranked by these averages. The 47 rank-ordered physicians were arbitrarily divided into low-, medium- and high-charge thirds so that ordering differences between inexpensive (low-charge), in-between (middle) and expensive (high-charge) physicians could be examined and compared. Summary information about the three groups was examined first (Table 1) without statistical testing because by definition the three groups differ at the summary level.

The next analysis step was comparing the frequencies with which physicians in each third ordered a specific laboratory test, x-ray examination, medication or a miscellaneous item. A large number of specific items were chosen for analysis to determine if "little ticket" ordering differences existed. The χ^2 statistic or, where applicable, the partition χ^{2}[16] was used to determine whether or not the three resident groups were alike in ordering frequency. Also, analyses of covariance and variance were used to examine several confounders.

Results

The total charge per clinic visit varied considerably among the physician groups (Table 1), even after prospectively selecting patients for chronic care of specific illnesses and after retrospectively controlling for several charge-influencing covariates. High-charge physicians average $67.52 (or 70%) more per visit than low-charge physicians, and they generated more charges than low-charge physicians in each category of charges except the visit fee, which was constant. Laboratory and drug category differences between high- and low-charge thirds were substantial ($10.71 and $45.74, respectively) and, when combined, explained 84% of the total $67.52 difference. High-charge physicians ordered laboratory, x-ray and drug category items during more of their visits, ordered more items once any was ordered and ordered more expensive items. They ordered consultations more frequently than low-charge physicians and ordered two or more consultations during a clinic visit with slightly greater frequency.

Next, many specific ordering decisions were examined. Because physician ordering of tests and drugs explained much of the variation among physicians, all 4,991 visits were examined for the ordering of 31 common laboratory tests and 114 common drugs. After grouping the ordered item into 17 laboratory test groups and 17 drug groups (Table 2), χ^2 testing was done. For 19 of the 34 groups of items, significant ($P < .05$) differences among the three resident groups were seen, with more frequent ordering by high-charge physicians. For the remaining 15 groups, high-charge physicians ordered items more frequently than low-charge physicians in eight of the groups and less in only five.

Table 3 displays ordering decisions that specifically relate to one of the four study diagnoses. Physician ordering of laboratory, x-ray, miscellaneous and drug items from 20 groups was subjected to 20 χ^2 tests. In 13 of the tests, significant differences were observed among the physician groups; in only two did low-charge physicians order more than high-charge physicians. Low-charge physicians treated more patients who had hypertension with diuretics alone and treated more patients who had degenerative joint disease with aspirin or acetaminophen rather than with nonsteroidal anti-inflammatory drugs. Both of these choices led to less expensive care.

High-charge physicians ordered an SMA 6 chemistry panel or a potassium measurement during more of the visits for hypertension than did low- and medium-charge physicians. Once they ordered either, they chose the more expensive of the two (serum potassium charge, $5.50; SMA 6 charge, $41.00 [1978 UNM charges]) significantly more often ($P < .001$). For visits for diabetes mellitus, high-charge physicians ordered nonfasting serum glucose testing much more frequently. For visits for congestive heart failure, medium- and high-charge physicians ordered chest x-ray films and serum digoxin measurements more frequently, but use of digoxin medication did not significantly vary among the three groups. Finding variation in the use of blood digoxin measurements prompted us to also examine the ordering of blood theophylline determinations. During visits where theophylline medication was ordered, progressively more blood theophylline measurements were requested across physician groups: low 4.8%, medium 11.1%, high 22.4% (χ^2 $P < .01$).

After doing these analyses, we considered the influence of three potentially confounding factors: physician decisions about when a patient should return to clinic, the number of visits occurring for each patient during the study and physician decisions to admit a patient to hospital during the clinic visit.

Physicians in the high-charge group prescribed a longer return appointment interval (64.1 days) than did medium- (61.1 days) and low- (58.4 days) charge physicians. Conceivably, they were more expensive because they lumped more prescribing and testing activity into fewer visits. However, when the influence of return appointment interval on total visit charges was isolated and examined with analysis of covariance, its separate effect on the per visit charge was only 27 cents per day. Thus, the 5.7-day difference in return appointment intervals between high- and low-charge groups could only account for $1.54 of the per visit charge difference ($67.52) between high- and low-charge physicians.

The average number of visits occurring for each patient during the study varied among the physician groups (high, 3.5 visits per patient, medium, 4.0, and low, 4.2). Because a larger number of visits for each patient might suggest greater illness and expense or, alternately, greater physician familiarity with the patient and less expense, these findings were analyzed further. Analysis of variance results on Table 4 show that when the effects of the number of visits per patient and the physician groups were examined simultaneously, the visit

number did not modify the big differences seen among physician groups in average clinic charges.

Although the study excluded charges resulting from a decision to admit a patient to hospital as part of the clinic visit, that decision could affect other clinic ordering decisions. Because this decision occurred only four times in 4,991 encounters, hospital admission decisions were not felt to be a source of bias.

Finally, several resident physician characteristics were examined. More of the low-charge residents were present both years of the project (they therefore accrued more clinic visits) and more of the high-charge group were third-year residents (they were slightly less expensive before the analysis of covariance adjustment), but the effect of these differences was minimized by the analysis of covariance adjustment. In each third the number of AOA residents (Alpha Omega Alpha—medical school honorary status) and the number eventually completing internal medicine residency were compared and found to be insignificantly different. Using departmental resident evaluations, two faculty members attempted to rank residents by their competence and performance, but agreement between the two raters was so low that it was not feasible to relate competence or performance assessments with clinic charge rankings.

Discussion

We found that the physicians in this study varied considerably in the frequency with which they ordered laboratory and x-ray tests, medications and miscellaneous services for patients with similar chronic health problems. As a result, patients of high-charge physicians incurred 70% more in charges than did those of low-charge physicians, and the average charge per visit for the highest charge physician was 3½ times that of the lowest charge physician. This amount of ordering variation among physicians was consonant with that reported by other authors cited in the introduction.

Our most important contribution was describing more specifically how low-, medium- and high-charge

TABLE 2.—*Ordering Frequencies of Physician Groups (Low-Charge, Medium-Charge and High-Charge) During All Clinic Visits*

Items Ordered	*Percentage of Total Visits During Which Specific Items Were Ordered*			χ^2
	Low	*Medium*	*High*	*P Value*
Total clinic patient visits, No.	1,862	1,449	1,680	
Laboratory tests				
CBC or Hct/Hb	7.7	9.0	15.4	<.0001
SMA 6	6.7	7.2	12.5	<.0001
Serum iron/TIBC, B_{12} or folate	1.7	1.2	1.7	NS
WBC differential	1.3	2.1	2.5	<.05
Platelet count	0.6	0.9	2.0	<.0005
Prothrombin time	1.0	1.3	2.5	<.005
Thyroid function test	3.3	4.6	5.7	<.005
Serum calcium	1.0	1.0	3.3	<.0001
Serum GOT	1.6	1.9	3.4	<.001
Serum creatinine	3.6	3.0	8.2	<.0001
Serum LDH	0.5	0.4	0.4	NS
Serum magnesium	0.2	0.0	0.4	NS
Serum cholesterol/triglyceride	1.2	0.7	0.7	NS
Stool tests for occult blood	1.5	2.2	1.4	NS
Urine analysis	6.8	8.3	9.6	NS
Urine culture	3.5	3.9	5.2	<.05
Creatinine clearance	0.1	0.1	0.2	NS
Drugs				
Allopurinol	1.6	1.0	3.0	<.005
Antacids	7.6	7.1	8.7	NS
Antianxiety and hypnotic agents	7.7	16.0	18.2	<.005
Antibiotics, oral	3.5	4.3	6.1	<.005
Antidepressants	4.0	5.2	5.3	NS
Bronchodilators	3.6	6.7	6.4	<.005
Cardiac medications, excluding digoxin	3.8	5.0	7.0	<.005
Drugs for symptoms of URI	5.1	5.0	9.1	<.0001
Estrogens, oral	1.1	1.2	1.7	NS
Multivitamins	4.5	4.4	4.5	NS
Over-the-counter medications	16.3	14.8	17.2	NS
Steroids, oral	0.8	0.6	0.7	NS
Steroids, topical	1.7	2.4	2.3	NS
Stool softeners	6.4	5.4	8.1	<.01
Thyroid hormones	5.0	7.0	6.2	<.05
Topical, nonsteroid dermatologics	2.7	1.7	2.0	NS
Warfarin	0.5	1.0	1.7	<.005

CBC = complete blood count; Hct/Hb = hematocrit/hemoglobin; SMA 6 = determinations of serum creatinine or glucose, urea nitrogen, chloride, carbon dioxide, sodium and potassium levels; TIBC = total iron-binding capacity; WBC = leukocyte count; GOT = aspartate aminotransferase (glutamic oxaloacetic transaminase); LDH = lactic dehydrogenase; URI = upper respiratory tract infection; NS = not significant

physicians vary. We found the expensive ordering behavior of high-charge physicians spread across all decisions. They ordered items or services during more visits, ordered more items once any were ordered and ordered slightly more expensive items. Even when they ordered some items—such as antianxiety drugs—much more frequently, such differences could only explain 6% of the total charge difference between high and low physician groups. For many of the ordering decisions examined, the magnitude of ordering variation among physicians was small and occasionally insignificant, but these differences occurred so regularly that the sum of the differences was great. We therefore conclude that a reasonable source of expensive ordering behavior is the cumulative cost of ordering "little ticket" items.

In examining ordering and prescribing variation among different physicians, investigators have used a variety of approaches to minimize the variation caused by patient-case mix and illness severity: a large sample size,[1,5,7] differentiating acute and chronic conditions,[4] examining a broad range of decisions,[7] prospectively selecting patients with a uniform diagnosis[9] and using the same patient in two different clinic settings.[11] This investigation combined four of these approaches (prospectively selecting patients by diagnosis, studying the care of only chronic conditions, using a large sample size and examining a broad range of clinical decisions). In addition, retrospective control of several covariates was done before analysis, and, finally, physician differences were examined by comparing physician groups rather than by comparing the highest and lowest charge physicians. Despite all these steps, substantial variation among physicians remained.

It is possible that some of this variation still resulted

TABLE 3.—*Ordering Frequencies of Physician Groups (Low-Charge, Medium-Charge and High-Charge) During Diagnosis-Specific Clinic Visits*

Disorder and Items Ordered	*Percentage of Diagnosis-Specific Visits During Which Specific Items Were Ordered*			χ^2 *P Value*
	Low	*Medium*	*High*	
Hypertension				
Clinic visits, No.	1,191	834	1,007	
Laboratory tests				
SMA 6 or serum potassium	20.7	25.3	30.2	<.0001
SMA 6 (includes potassium)	6.8	8.0	14.2	<.001
Serum potassium	13.9	17.3	16.0	
X-ray films				
Chest	3.8	7.7	6.3	<.001
Miscellaneous				
Electrocardiogram	3.9	4.9	6.1	NS
Drugs				
Potassium	23.8	21.2	21.5	NS
Diuretics only	47.2	48.4	41.7	<.01
Nondiuretic, antihypertensives also	33.7	35.3	40.4	
Diabetes Mellitus				
Clinic visits, No.	507	475	557	
Laboratory				
Urine analysis	10.1	11.2	11.3	NS
Any serum glucose test	56.8	72.4	76.4	<.005
SMA 6 (includes glucose)	7.9	6.9	13.3	<.001
Random	8.9	24.6	20.1	<.0001
Fasting	39.8	39.8	39.9	NS
Two-hour postprandial	0.2	1.1	2.9	<.001
Congestive Heart Failure				
Clinic visits, No.	322	252	266	
Laboratory test				
Digoxin level	6.8	7.9	15.4	<.005
X-ray films				
Chest	20.2	43.1	47.8	<.001
Drugs				
Digoxin	59.3	61.1	55.6	NS
Degenerative Joint Disease (DJD)				
Clinic visits, No.	513	387	582	
Laboratory test				
Antinuclear antibody	0.4	2.0	2.8	<.05
X-ray films				
One or more joint films	3.5	8.0	6.7	<.05
Drugs				
Antacids	12.3	12.9	12.7	NS
Some DJD drug therapy	56.2	59.8	62.7	NS
Aspirin/acetaminophen only	27.1	18.6	11.3	<.0001
Nonsteroidal anti-inflammatory	29.1	41.2	51.4	

SMA 6 = determinations of serum creatinine or glucose, urea nitrogen, chloride, carbon dioxide, sodium and potassium levels; NS = not significant

TABLE 4.—*Charges per Clinic Visit by Physician Groups (Low-Charge, Medium-Charge and High-Charge) and by Number of Visits per Patient*

Number of Visits per Patient During the Study	Average Charge per Clinic Visit (Number of Patients) Low $ (No.)	Medium $ (No.)	High $ (No.)
1	111 (89)	106 (69)	147 (96)
2	88 (77)	124 (56)	141 (90)
3	99 (72)	121 (84)	149 (76)
4	107 (56)	126 (46)	162 (58)
5	108 (51)	131 (33)	162 (38)
6 or more	105 (134)	126 (85)	168 (74)

Analysis of variance: physician charge group effect, $P < .0001$; number of visits per patient effect, $P = .18$.

from patients' needs or study biases rather than physician decisions. Our measures of and controls for diagnostic and illness complexity were limited to what is obtainable from the medical record, the 1,284 study patients could not be randomly assigned to physicians and physicians were not blind to the investigation. Although imperfect, we feel that our control for bias was the best so far accomplished in this type of investigation and sufficient to conclude that "little ticket" use is primarily due to physician ordering behavior rather than patient needs and wants.

Like illness severity, measuring quality of care is difficult. Inferences about increased or decreased quality among the three groups of residents can be made, but correlating the diffuse ordering characteristics of high-charge physicians with similarly diffuse improvements in quality would be unlikely and difficult to quantitate, especially at the outcome level. In the past, associations between quality variation and ordering variation have not been found[9,17] or have been equivocal.[12]

The "little ticket" ordering habit has implications for cost containment and medical education. Because this ordering behavior pervades all decisions, it suggests that basically different analytic or decision-making styles distinguish expensive and inexpensive physicians. Therefore, cost-containment efforts focused only on specific decisions, such as test ordering, may not have lasting effects. On the other hand, changing an expensive physician's fundamental style would affect the ordering of many services. Analytic or decision-making styles are undoubtedly influenced by many factors,[18,19] including "personality traits."[20] Tolerance of uncertainty is a trait hypothesized to influence expensive ordering habits (intolerance)[5,19,21-23] and, possibly conversely, inexpensive habits (overtolerance ?). Investigators have found less ordering among physicians with greater experience or more training[4,5,12,15,24] and no association between professional characteristics—that is, board certification—and ordering habits.[4,5,8,12,16] This may indicate that professional training cannot or has not adequately addressed these issues. Improved understanding of the relationships among personality, decision-making styles and professional training may be very important in controlling costs without sacrificing quality.

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Containing Costs in the Treatment of Congenital Heart Disease

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In the Congenital Heart Program at San Diego Children's Hospital, alterations in medical practice have reduced costs without impairing quality or access. Pediatric cardiac catheterization was done in 483 consecutive elective patients without overnight hospital stay. Hospital readmission was required in one patient for psoas tendinitis. Avoiding overnight hospital stay minimized attendant risks of hospital care, lessened psychosocial trauma and reduced the average hospital bill by $493 (29%). Hospital stay was also reduced for elective surgical correction of congenital heart disease on a case-by-case basis. Review of 151 consecutive cases (1978 through 1982) showed a decrease in both preoperative days in hospital and postoperative days in an intensive care unit. The duration of the postoperative stay was shortened from 6.8 days in 1978-1979 to 4.4 days in 1982 ($P < .05$). No increase in morbidity and no mortality resulted from the shortened perioperative hospital stay. Financial savings from this process averaged $991 per procedure.

Diagnostic tests were reassessed and many precatheterization laboratory tests were eliminated. Without change in new patients seen or surgical volume, the use of cardiac catheterization decreased from 241 procedures in 1981 to 161 in 1982 and the number of operations without catheterization increased (11 to 22, 1981 to 1982). No increase in surgical morbidity or mortality was found comparing those diagnosed only by echocardiography with those who had preoperative cardiac catheterization. The decrease of 80 catheterizations in one year resulted in a savings of $188,800.

True cost containment (reducing cost without reducing quality) can be accomplished in congenital heart programs. Similar cost containments in other disciplines may also be achieved.

(Waldman JD, George L, Lamberti JJ, et al: Containing costs in the treatment of congenital heart disease [Costs of Care]. West J Med 1984 Jul; 141:123-126)

The recent crisis in health care financing has caused both health care professionals and the public to become more aware of the costs of modern high-technology medical care. Health planners now seek to reduce expenditures while preserving quality and access. For the past seven years, strategies have been implemented in the Congenital Heart Program at San Diego Children's Hospital that have reduced cost without impairing quality. Our experience is summarized herein for two reasons: (1) to share our specific approaches with other physicians caring for children who have congenital heart disease and (2) to stimulate physicians in other disciplines to reassess their modes of practice.

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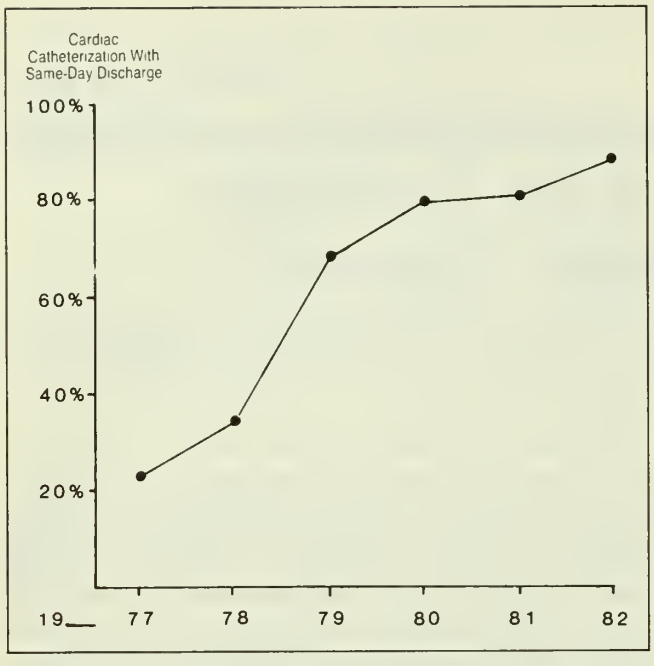

Figure 1.—Same-day discharge for cardiac catheterization, 1977 through 1982 at San Diego Children's Hospital. A gradual increase in same-day discharge is seen from 1977 to 1980, whereas in 1980 through 1982, the percentage has not varied significantly from 80%.

Reducing Hospital Stay

Our practice of cardiac catheterization and cardiovascular surgical procedures was reassessed based on the premise that any reduction in hospital stay is medically (and financially) beneficial if it does not increase patient risk.

Cardiac Catheterization

In the past, children were routinely admitted to hospital the day before cardiac catheterization and discharged the day after because of (1) the need for precatheterization tests such as electrocardiogram (ECG), complete blood count, chest x-ray, echocardiogram and the like; (2) the workup of the patient by physician(s)-in-training; (3) the preference of cardiologists to start catheterizations in the early morning, and (4) the need to observe the patient after the study.

In an article recently published in the *American Journal of Cardiology*,[1] we assessed a program of cardiac catheterization without overnight hospital stay during the years 1977 through 1980. Since that time, we have continued to do catheterizations with "same-day discharge." For the seven-year period ending in December 1982, 1,047 pediatric heart catheterizations were done at our center, of which 714 were elective studies. In all, 68% (483/714) were done on a same-day discharge basis (Figure 1) with the percentage rising each year (to 89% in 1982). There was one complication (1/483) noted in the 1982 paper in which a child required readmission because of psoas tendinitis. Thus, pediatric cardiac catheterization can be done safely—in selected patients—on a same-day-discharge ("outpatient," in a sense) basis. Our earlier study showed a 29% decrease in the hospital bill resulting from a reduction of almost $500 in room charges. This translates to a savings of more than $240,000 ($500 × 483) since 1977 by the same-day-discharge approach.

Admission to Hospital for Operation

Initially, surgical patients were routinely admitted two days before the procedure and were discharged whenever they seemed ready to resume relatively normal activities. Beginning in 1979, we began to reduce the length of preoperative and postoperative hospital stays on an individual basis.

A total of 151 consecutive cases from September 1978 through December 1982 were reviewed in which a child had surgical correction of uncomplicated congenital heart disease. The following lesions were chosen for review: ventricular septal defect (45 patients), atrial septal defect (43 patients), patent ductus arteriosus (39 children admitted to hospital solely for the operation, thus excluding neonates) and tetralogy of Fallot (24 patients).

A gradual decrease occurred in preoperative hospital stay. In 1978, 42% of patients were admitted two or more days before the surgical procedure. In part, this reflected the approach of catheterization and operation on one admission. As the same-day-discharge posture towards catheterization became standard, the "cath and surgery on one admission" system no longer was appropriate. By 1982, 99% of all patients reviewed (36/37) were admitted the day before the surgical procedure.

Postoperative length of stay decreased in two ways. First, the amount of time after the operation spent in the cardiac surgical intensive care unit decreased from 3.0 days (in 1978-1979) to 2.1 days in 1982 ($P<.05$); the change was most apparent in the tetralogy of Fallot group where the average stay in the surgical intensive care unit decreased from 4.0 days in 1978-1979 to 2.3 days in 1982. Second, the total postoperative hospital stay (Figure 2) decreased from 6.8 days (average for the total group) to 4.4 days in 1982 ($P<.05$).

No complications were noted that were directly attributable to an early hospital discharge. Three patients (3/151, 2%) required hospital readmission within 30 days of the operation, two for pericarditis and one with pneumonia.

Besides the beneficial psychosocial effect of decreasing the hospital stay, costs were reduced by less time in the surgical intensive care unit and in hospital in general. The result was a decrease in room charges at our institution of about $991 per elective surgical procedure; this calculation does not include secondary reductions in ancillary charges (laboratory, drugs, respiratory therapy and so forth).

Changes in Diagnostic Studies

Before Catheterization

In the past, the following tests were routinely done immediately before cardiac catheterization: complete

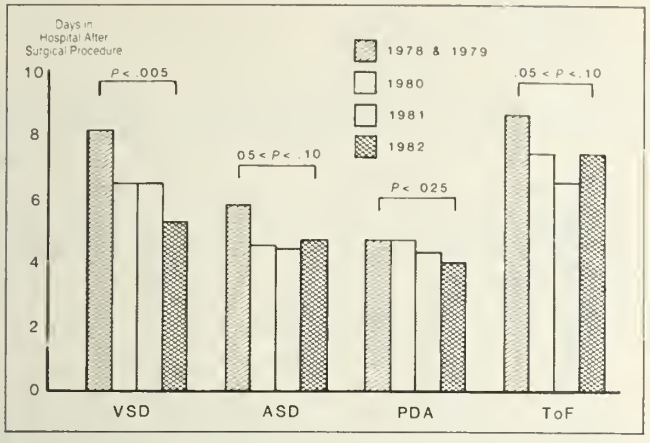

Figure 2.—Change in length of hospital stay after surgical repair of congenital heart disease—1978 through 1982—at San Diego Children's Hospital. A gradual decrease in hospital stay is seen in all surgical groups; the changes are significant in the VSD and PDA groups. VSD = ventricular septal defect, ASD = atrial septal defect, PDA = patent ductus arteriosus, ToF = tetralogy of Fallot

blood count, electrolytes, prothrombin time and partial thromboplastin time, urine analysis, x-ray study of chest, ECG and echocardiogram. Currently we do hemoglobin and hematocrit, chest roentgenogram, ECG within one week of study, echocardiogram within one month of catheterization and a dipstick test of urine on the ward. Eliminating the laboratory tests as noted resulted in a savings (at current prices) of $159.75 per catheterization. We have found no instance—in more than 1,000 catheterizations done in the past seven years—wherein the "routine" test eliminated would have provided clinically necessary information.

Substituting Echocardiography for Catheterization

At San Diego Children's Hospital, two-dimensional echocardiography began to be used in early 1980 but pulsed Doppler technology was not fully operating until late 1981. A comparison of our 1981 and 1982 clinical experience (Table 1) showed a major effect of echocardiography in the use of cardiac catheterization. Without significant change in patient volume or number of surgical procedures done, the catheterization volume decreased by 33% (from 241 to 161) and operation without catheterization doubled (11 to 22).

During the three-year period of 1980 through 1982, 394 cardiovascular operations were done at our center. Of these, 40 patients were operated on without preoperative catheterization: 18 neonates and 11 older children with patent ductus arteriosus, 6 with atrial septal defect, 3 with critical semilunar valve stenosis, 1 with critical coarctation and 1 1,700-gram infant with obstructed total anomalous pulmonary venous connection. Surgical mortality was 4% in those with prior catheterization (15/354) and 2.5% without preoperative catheterization (1 case of critical aortic stenosis in 40 patients).

The charge for a complete echocardiographic examination is $350; for a complete cardiac catheterization, the charge is $2,710. Thus, the decrease of 80 catheterizations at our center translated into a savings of $188,800 (80 × [2,710 − 350]). In addition to financial savings, substituting echocardiography for catheterization eliminated the risk of ionizing radiation,[2] psychosocial trauma[3,4] and the like.

TABLE 1.—*Comparison of Clinical Experience for 1981 and 1982 at the San Diego Children's Hospital*

Patients and Procedures	*Number*	
	1981	*1982*
New patients	945	978
Cardiovascular operations	128	125
Cardiac catheterizations	241	161
Operation without catheterization	11	22

Discussion

Ginzberg defines true cost containment as "A reduced inflow of real resources into the health care system without a diminution in useful output that would adversely affect the satisfaction of patients or their health status."[5] We believe this is possible and our strategies in the care of patients with congenital heart disease have reduced cost without impairing quality.

The first step to develop cost-containment plans is to ask why one does what one does, especially habitual or routine activities. For instance, we asked

- Does cardiac catheterization require a stay in hospital for two nights?
- Are a complete blood count, urine analysis and electrolyte panel necessary before every cardiac catheterization?
- Must all patients have catheterization before their surgical procedure?
- Must a patient be kept in hospital for 10 to 14 days for an elective operation on the heart?

Ultimately, these questions were all answered negatively.

It is axiomatic that any reduction in hospital stay may be beneficial by reducing the disadvantages of being in hospital—that is, nosocomial infection, diagnostic or therapeutic errors, psychosocial trauma and expense.[6] However, any inpatient procedure changed to outpatient status or any reduction in usual length of hospital stay must be shown not to increase morbidity or mortality.

In 1976 the concept of pediatric cardiac catheterization with same-day discharge ("outpatient catheterization") was considered radical and dangerous. Now patients are rarely kept overnight; the safety of the process has been confirmed. Both families and patients attest to the psychosocial benefits. Same-day discharge thus safely reduces both hospital stay and cost.

In surgical patients, the same principle produced larger savings because greater reduction in hospital stay could be achieved. Again, the data indicated that in

properly selected patients, early hospital discharge (four to five days after heart operation) could be done safely.

After reassessing our diagnostic methods, it was found that most routine laboratory studies before catheterization were not needed. In the absence of a history of bleeding disorders, renal or urinary tract symptoms or recent infection, laboratory studies in these areas were unnecessary and costly. It must be emphasized that a history is still critical, especially if one eliminates routine laboratory work. In a teenage girl, to neither check last menstrual period nor screen for pregnancy is unconscionable.

In most treatment centers for congenital heart disorders, almost all patients have preoperative cardiac catheterization. Exceptions are made, however, for patent ductus arteriosus in premature infants and coarctation of the aorta in older children. Rice and coworkers at the Mayo Clinic[7] challenged this approach and reported their experience with echocardiography as the primary diagnostic modality in neonates with suspected heart disease. In a consecutive series of 40 neonates who presented with possible congenital heart disease, catheterization was not needed in 26 (65%), including 8/40 (20%) who had surgical repair without catheterization. There were no significant diagnostic errors (either false-positive or false-negative) noted in their experience, and they concluded "no longer is cardiac catheterization necessarily the primary means for anatomic diagnosis of congenital cardiac malformations in the newborn."

At San Diego Children's, the substitution of echocardiography for cardiac catheterization was stimulated by the same self-analytic process as previously mentioned. We questioned the need to catheterize a patient who has a heart defect such as atrial septal defect, atrioventricular canal, coarctation of the aorta or critical aortic stenosis. Increasingly, the information available by echocardiography was considered clinically complete. Eliminating catheterization in selected patients resulted in a decreased risk to those patients and significant financial savings. The surgical outcome data confirmed the absence of increased mortality in those selected for operation without catheterization. Our experience corroborates and expands the conclusion of the Mayo Clinic group[7] that catheterization can be avoided in many instances. A similar conclusion has been drawn at the Hospital for Sick Children in Toronto (R. M. Freedom, MD, and J. F. Smallhorn, MD, May 1983, verbal communication) where during the past several years the surgical volume has increased, the surgical mortality is unchanged and the catheterization volume has decreased from 905 in 1977 to 621 in 1982, directly attributable to echocardiography. Thus, true cost containment can be achieved by substituting echocardiography for cardiac catheterization in selected patients.

Conclusions and Implications

The specific strategies reported herein seem applicable to other centers dealing with children who have congenital heart disease and significant savings will likely result from more widespread applications of these approaches. Reassessing practice modes in other high-technology, hospital-oriented disciplines will also likely result in different ways to achieve high-quality medical care at reduced cost.

Caveat Magister

Repeatedly in this paper the phrase "selected patients" was used. We cannot emphasize too strongly that the safety of any innovative procedure requires appropriate patient selection by the responsible physicians. To enact blanket proposals such as "all children will have outpatient catheterization," "cardiac catheterization is unnecessary in patients with atrial septal defect" or "children will be discharged five days postoperatively" would preempt a physician's ability to provide adequate care for an atypical patient. Cost-containment proposals should be formulated by medical professionals and allow leeway to optimize care for unusual patients.

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In Memoriam

California Medical Association

BLAISDELL, FRANK E., JR., Watsonville. Died January 11, 1984, in Watsonville, aged 87. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Dr Blaisdell was a retired member of the Santa Cruz Medical Society.

BURCHFIEL, ROBERT D., San Jose. Died January 16, 1984, in San Jose, aged 62. Graduate of Washington University School of Medicine, St Louis, 1950. Licensed in California in 1951. Dr Burchfiel was a member of the Santa Clara County Medical Society.

CARTER, KENNETH L., Sacramento. Died December 8 1983, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1944. Dr Carter was an associate member of the Sacramento-El Dorado Medical Society.

CHERVIN, MAX EARL, Covina. Died January 30, 1984, aged 59. Graduate of Indiana University School of Medicine, Indianapolis, 1948. Licensed in California in 1954. Dr Chervin was a retired member of the Los Angeles County Medical Association.

CLARK, AUSTIN M., Palo Alto. Died July 17, 1983, in Petaluma of carcinoma of the lung, aged 74. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1935. Licensed in California in 1935. Dr Clark was an associate member of the Santa Clara County Medical Society.

CLINITE, WILLIAM D., Tulare. Died November 18, 1983, in Tulare of cancer, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1939. Dr Clinite was an associate member of the Tulare County Medical Society.

CORLEY, CHARLES L., Sonoma. Died February 17, 1984, in Sonoma of heart disease, aged 71. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1951. Licensed in California in 1952. Dr Corley was a member of the Sonoma County Medical Association.

CUNEO, HENRY M., Los Angeles. Died December 6, 1983, aged 76. Graduate of Baylor University College of Medicine, Dallas, 1937. Licensed in California in 1938. Dr Cuneo was an associate member of the Los Angeles County Medical Association.

DIESNER, HOWARD G., Sunnyvale. Died January 18, 1984, in Sunnyvale, aged 75. Graduate of the University of Illinois College of Medicine, Chicago, 1933. Licensed in California in 1933. Dr Diesner was a retired member of the Santa Clara County Medical Society.

DILLER, THEODORE, San Francisco. Died January 7, 1984, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr Diller was a retired member of the San Francisco Medical Society.

DUNN, GEORGE P., San Francisco. Died February 2, 1984, aged 68. Graduate of the Creighton University School of Medicine, Omaha, 1942. Licensed in California in 1947. Dr Dunn was a retired member of the San Francisco Medical Society.

FAINER, DAVID C., Ventura. Died December 7, 1983, in Ventura of brain tumor, aged 61. Graduate of the University of California Medical School, Berkeley-San Francisco, 1947. Licensed in California in 1948. Dr Fainer was an associate member of the Ventura County Medical Society.

FLYNN, PAUL F., Oakland. Died February 13, 1984, aged 61. Graduate of Tufts College Medical School, Boston, 1948. Licensed in California in 1957. Dr Flynn was a member of the Alameda-Contra Costa Medical Association.

GREENE, WILLIAM B., Bakersfield. Died December 23, 1983, in Bakersfield of myocardial infarct, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1949. Dr Greene was a member of the Kern County Medical Society.

GUERRA, ARTHUR L., Alameda. Died October 21, 1983, aged 93. Graduate of Georgetown University Medical School, Washington, 1914. Licensed in California in 1922. Dr Guerra was a retired member of the Alameda-Contra Costa Medical Association.

HAUSER, ARNOLD E., Napa. Died February 17, 1984, in Napa, aged 90. Graduate of Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Germany, 1920. Licensed in California in 1939. Dr Hauser was a retired member of the Napa County Medical Society.

HAYES, PAUL, Palm Desert. Died September 10, 1983, aged 79. Graduate of the University of Maryland School of Medicine, Baltimore, 1928. Licensed in California in 1958. Dr Hayes was a retired member of the Alameda-Contra Costa Medical Association.

JOHNSON, DANIEL H., Yucaipa. Died March 29, 1984, in Redlands of bleeding ulcers, aged 54. Graduate of the University of Manitoba Faculty of Medicine, Edmonton, 1957. Licensed in California in 1964. Dr Johnson was a member of the San Bernardino County Medical Society.

JOYA, KENNETH M., Auburn. Died January 5, 1984, in Sacramento of ruptured aortic aneurysm, aged 70. Graduate of Creighton University School of Medicine, Omaha, 1937. Licensed in California in 1941. Dr Joya was a retired member of the Placer-Nevada County Medical Society.

KOCHER, RUDOLPH A., Carmel. Died December 17, 1983, in Monterey, aged 100. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1912. Licensed in California in 1920. Dr Kocher was an associate member of the Monterey County Medical Society.

KROHN, LEON, Los Angeles. Died June 9, 1983, aged 76. Graduate of Northwestern University Medical School, Chicago, 1930. Licensed in California in 1937. Dr Krohn was an associate member of the Los Angeles County Medical Association.

MAPES, CLINE NEVILLE, San Bernardino. Died December 12, 1983, in San Bernardino, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1944. Licensed in California in 1944. Dr Mapes was a member of the San Bernardino County Medical Society.

MERKEL, GILES G., San Francisco. Died October 16, 1983, in Minnesota of an aneurysm, aged 54. Graduate of the University of Minnesota Medical School, Minneapolis, 1954. Licensed in California in 1959. Dr Merkel was a member of the San Francisco Medical Society.

PATTON, THOBURN G., Rialto. Died December 6, 1983, aged 55. Graduate of the University of Illinois College of Medicine, Chicago, 1955. Licensed in California in 1956. Dr Patton was a member of the San Bernardino County Medical Society.

PETERSON, LAWRENCE J. P., Lodi. Died November 6, 1983, in Exira, Iowa of myocardial infarct, aged 83. Graduate of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Dr Peterson was an associate member of the San Joaquin County Medical Society.

PILE, DUANNE F., Santa Rosa. Died March 13, 1984, in Santa Rosa of brain tumor, aged 63. Graduate of the University of Illinois College of Medicine, Chicago, 1944. Licensed in California in 1945. Dr Pile was a member of the Sonoma County Medical Association.

SMITH, HARRY F., San Bruno. Died February 17, 1984, in Hillsborough of heart disease, aged 71. Graduate of the University of Rochester School of Medicine and Dentistry, 1938. Licensed in California in 1938. Dr Smith was a retired member of the San Mateo County Medical Society.

WILLIAMS, LAWRENCE B., Santa Barbara. Died December 3, 1983, in Santa Barbara, aged 60. Graduate of State University of Iowa College of Medicine, Iowa City, 1948. Licensed in California in 1963. Dr Williams was a member of the Medical Society of Santa Barbara County.

WILSON, LEO L., San Jose. Died February 5, 1984, in Santa Barbara, aged 80. Graduate of Creighton University Medical School, Omaha, 1927. Licensed in California in 1943. Dr Wilson was a retired member of the Santa Clara County Medical Society.

YONAN, MARSHAL E., San Francisco. Died December 25, 1983, aged 82. Graduate of Illinois Medical College, Chicago, 1930. Licensed in California in 1930. Dr Yonan was a retired member of the San Francisco Medical Society.

New Mexico Medical Society

MAISEL, ALBERT L., Albuquerque. Died August 25, 1983, in Albuquerque, aged 70. Graduate of Jefferson Medical College, Philadelphia, 1939. Licensed in New Mexico in 1939. Dr Maisel was an emeritus member of the Albuquerque & Bernalillo County Medical Association.

Washington State Medical Association

BROOKE, J. ROBERT, Tacoma. Died March 2, 1984, in Tacoma, aged 73. Graduate of McGill University Faculty of Medicine, Montreal, 1938. Licensed in Washington in 1939. Dr Brooke was a member of the Pierce County Medical Society.

CANTRELL, JAMES R., Seattle. Died November 11, 1983, in Seattle, aged 61. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1946. Licensed in Washington in 1960. Dr Cantrell was a member of the King County Medical Society.

DUERFELDT, TREACY H., Tacoma. Died December 22, 1983, in Tacoma, aged 82. Graduate of Rush Medical College, Chicago, 1930. Licensed in Washington in 1931. Dr Duerfeldt was a retired member of the Pierce County Medical Society.

KOSTERLITZ, HANNA, Seattle. Died May 19, 1983, in Seattle, aged 84. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, 1925. Licensed in Washington in 1937. Dr Kosterlitz was a member of the King County Medical Society.

REGAN, CHESTER, Seattle. Died in March 1984 in Seattle, aged 89. Graduate of the University of Minnesota Medical School, Minneapolis, 1924. Licensed in Washington in 1925. Dr Regan was a retired member of the King County Medical Society.

SPRECHER, EDWIN E., Seattle. Died August 10, 1983, aged 68. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1940. Licensed in Washington in 1942. Dr Sprecher was a retired member of the King County Medical Society.

YOUNG, WILLIAM ALEXANDER, Seattle. Died January 15, 1984, in Seattle, aged 63. Graduate of St Louis University School of Medicine, 1945. Licensed in Washington in 1947. Dr Young was a member of the King County Medical Society.

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Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

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Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

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Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

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(Continued from Page 51)

July 26-28—**General Surgical Update 1984.** Albuquerque. Thursday-Saturday. Marriott Hotel. 15 hrs. AMA Cat. I, NM Cat. IV. Contact: UNM School of Medicine, Office of CME, Albuquerque 87131. (505) 277-3942.

August 26-31—**Abandonment.** Abiquiu. Sunday-Thursday. Ghost Ranch. 36 hrs. NM Cat. IV. Contact: Chicago Society of Jungian Analysts, Inter-Regional Society of Jungian Analysts, 1520 Cerro Gordo Rd., Santa Fe 87501. (505) 982-5693.

November 9-10—**New Mexico Medical Society Interim Meeting—Sports Medicine.** Clovis. Friday-Saturday. 8 hrs. AMA Cat. I, NM Cat. IV. Contact: NMMS, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. NM and AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center,

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * *

EMERGENCY MEDICINE

November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

SURGERY

November 30-December 1—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

September 7-8—**The Ashland Conference: Immunology and Allergy in Primary Care.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7:00 a.m. to 9:00 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE GRAND ROUNDS

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Wednesday—8:00 a.m. to 9:00 a.m. Contact: Thomas Schwenk, MD, (801) 581-8633.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8:00 a.m. to 9:00 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8:00 a.m. to 9:00 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30 a.m. to 8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext. 2143).

* * *

July 15-20—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, Wyoming. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art** (Sponsor: University of Utah). Wednesday. Jackson Lake Lodge, Wyoming. Contact: John D. Armstrong, MD, (801) 581-7553.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

(Continued on Page 142)

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ENDOCRINOLOGIST: Immediate opening in private practice. Exclusively subspecialty: Endo/Diabetes. Los Angeles. Reply with CV to Box 6421, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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CARDIOLOGIST: Invasive or non-invasive. Preferably speaks some Spanish. An opportunity to develop testing in a small community hospital and a private practice in California's Imperial Valley. Financial arrangements negotiable (rent subsidy, etc). Reply to Box 6432, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

THE OFFICE OF WORKERS' COMPENSATION PROGRAMS is seeking Board eligible/certified physicians to provide second opinion evaluations. Specialties include Orthopedics, ENT, Psychiatry, Cardiology, and Neurosurgery/Neurology. Locations include the San Francisco Bay Area, the Greater Los Angeles Area, San Diego, and Las Vegas. A contracted second opinion physician is precluded from also providing referee exams and is subject to fee schedule. Please send curriculum vitae to: Gerald T. Cullen, Contracting Officer, Office of Workers' Compensation Programs, US Dept. of Labor, 450 Golden Gate Ave., P.O. Box 36066, San Francisco, CA 94102.

ER PHYSICIAN needed for emergency departmen in small community hospital located on the coast 25 miles south of San Francisco. Reply: Dr Timothy Whelan, St. Catherine's Hospital, Moss Beach, CA 94038.

THE DEPARTMENT OF FAMILY MEDICINE at University of California, Irvine is recruiting for a Spanish-speaking Pediatrician with MPH degree and teaching experience. The appointment will be at the assistant professor level in the clinical series. Send curriculum vitae to: J. Dennis Mull, MD, Chairman, Department of Family Medicine, University of California, Irvine, 101 City Drive South, Orange, CA 92668. An Affirmative Action/Equal Opportunity Employer.

FAMILY PRACTICE PHYSICIANS and Primary Care Internists openings available in rural group practice in Northern California. Full or part time. Very competitive salary and good working conditions Contact (707) 829-0992.

(Continued on Page 144)

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In clinical anxiety,

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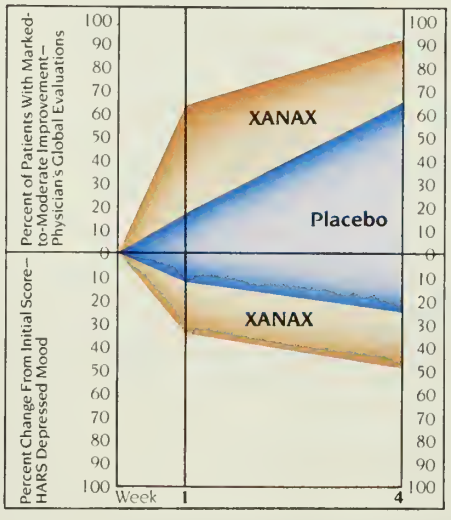
depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy
- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file. The Upjohn Company

Please see next page for brief summary of prescribing information

Xanax® 0.25 mg Tablets

alprazolam Ⓒ IV

XANAX® Tablets
(alprazolam) Ⓒ

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects.* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

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CONTINUING MEDICAL EDUCATION

(Continued from Page 138)

July 20—**Acute Abdominal Pain.** Seattle. Friday. Riverton Hospital. Contact: U/W.

July 22-26—**Annual Summer Meeting 1984. Washington State Academy of Ophthalmology.** Orcas Island. Sunday-Thursday. Rosario Resort. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

July 27—**Stress.** Seattle. Friday. Riverton Hospital. Contact: U/W.

July 27-29—**Seafair VI Pediatric Anesthesia and Intensive Care.** Seattle. Friday-Sunday. Seattle Sheraton. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave, Suite 900, Seattle 98121. (206) 623-4801.

August 17-23—(OREGON) **Psychiatry for Primary Physicians.** Friday-Thursday. Sunriver Resort, Sunriver. Contact: U/W.

August 29-September 4—(ALBERTA) **Scientific Aspects of the Art of Dance.** Banff Centre, Banff, Alberta. Contact: U/W.

September 5-6—**Recent Advances in Obesity.** Seattle. Wednesday-Thursday. Health Sciences Center. Contact: U/W.

September 6-7—**Symposium on Breast Disease.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

September 7-8—**Nutrition and Bone Metabolism.** Seattle. Friday-Saturday. Health Sciences Center. Contact: U/W.

September 8-15—(ALBERTA) **Neurosurgery of Pain.** Banff. Saturday-Saturday. Banff Park Lodge. Contact: U/W.

September 10-14—**Advances in Family Practice.** Seattle. Monday-Friday. Health Sciences Center. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

September 10-14—**Advances in Family Practice With ACLS Pathway.** Seattle. Monday-Friday. Health Sciences Center. Contact: U/W.

September 11-12—**Conference on Homeostatic Functions in the Elderly.** Sheraton St. Louis Hotel, St. Louis, MO. Contact: Sharon Smith, Conference Secretary, Geriatric Center (111G-JB), VA Medical Center, St. Louis, MO 63125. (314) 894-4659.

September 12-14—**Dermatologic Therapeutic Hotline.** Orcas Island. Wednesday-Friday. Rosario Resort. Contact: Paul H. Jacobs, MD, Department of Dermatology, Stanford University Medical Center, Stanford, CA 94305. (415) 497-7854.

September 13-16—**Washington State Medical Association Annual Meeting.** Seattle. Thursday-Sunday. Westin Hotel. Contact: Patti Smith, WSMA, 2033 Sixth Avenue, #900, Seattle 98121. (206) 623-4801.

September 26—**Advances in Lab Medicine.** Seattle. Wednesday. Health Sciences Center. Contact: U/W.

October 3-5—**Molecular Medicine.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

October 5—**Practical Pulmonary Function.** Seattle. Friday. Contact: VMMC.

October 12—**Frontiers in Eye Care for the Allied Professional.** Seattle. Friday. Contact: VMMC.

October 12-13—**Neurology Update.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

October 13—**Radiology Northwest.** Saturday. U/W Health Sciences Center. Contact: U/W.

October 19—**Annual Cancer Conference: Early Screening and Detection.** Seattle. Friday. Contact: VMMC.

October 25-26—**Advances in Internal Medicine.** Thursday-Friday. U/W Health Sciences Center. Contact: U/W.

November 1-2—**Washington Chapter—American College of Emergency Physicians.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, WACEP, 2033 Sixth Avenue, #900, Seattle 98121. (206) 623-4801.

November 9—**GI Update.** Seattle. Friday. Contact: VMMC.

December 7—**Practical Pediatrics.** Seattle. Friday. Contact: VMMC.

January 11—**Treatable Hepato-Biliary Disease.** Seattle. Friday. Contact: VMMC.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

WYOMING

July 15-20—**Summer Update in Clinical Microbiology and Immunology.** University of Utah at Jackson Hole. Sunday-Friday. 23 hrs. $350. Contact: John Matsen, MD, (801) 581-7480.

July 25—**Cardio-Thoracic Imaging/State of the Art.** University of Utah at Jackson Lake Lodge. Wednesday. Contact: John D. Armstrong, MD, (801) 581-7553.

September 9-15—**Effective Management of Common Sports Injuries: An EPIC Medical Expedition.** Bicycle touring through Yellowstone and Grand Teton National Parks. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

(Continued from Page 139)

BOARD CERTIFIED Oncologist, Cardiologist, Internist, Neurosurgeon, Otorhinoleryngologist for Southeastern Washington—Tri-Cities, 150,000 population. Outdoor activities abound. Group or solo opportunities. Contact Vesta Skiens, Kennewick General Hospital (509) 586-6111 (309).

INTERNIST, CALIFORNIA, two American trained, Board certified General Internists seek the same for association in busy practice in Central San Joaquin Valley city of 50,000. No investment required. Subspecialist with interest in doing some genaral Internal Medicine desirable. Excellent recreational area with access to San Francisco, Yosemite and coast. Opportunity to establish a busy independent practice with no initial investmant. Reply to: Box 6434, Western Journel of Medicine, 44 Gough St., San Francisco, CA 94103.

GENERAL SURGEON, Board certified/eligible: multispecialty group, university town central Washington, has space and services availabla on a leese or compensation basis with futura partnarship anticipated. Contact J. W. Devney, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

DERMATOLOGIST WANTED. Southern California. Board certified or eligible for permanent part-time two to three days weekly. Salary negotiable. Reply with CV to Box 6429, Western Journal of Madicine, 44 Gough St., San Francisco, CA 94103.

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F/T OB/GYN for growing multispecialty group in sunny L.A. Spanish very important. 1st year compansation negotiable. Partnership potential 2nd year. CV to Med. Dir. Box 6435, Wastern Journal of Madicine, 44 Gough St., San Francisco, CA 94103.

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NORTHERN CALIFORNIA: Physician, Board certified/qualified in Emergancy Medicina or Family Practice, to work 16-32 hours per week in a busy freestanding emergency center. Prefer someone interested in full-time position within 3-6 months. Competitive compensation, malpractice, and bonus for part-time position. Full-time position will also include health insurance, vacation, educational expenses and other benefits. Send CV and references to Joanne Berkowitz, MD, The Emergency Center Medical Group, 4948 San Juan Avenue, Fair Oaks, CA 95628.

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CLINICAS DEL CAMINO REAL, INC. is seeking two Family Practice Physicians to augment its medical practice. Pay range is $4,200 to $4,700 per month plus 3 weeks vacation, sick leave, tax deferrad plan, holidays and an excellent working environment located in Ventura County. Send résumé to Robert S. Juarez, Executive Director, PO Box 4878, Ventura, CA 93004. Bilingual Spanish/English desirable. An EOE.

OCCUPATIONAL MEDICINE PHYSICIAN: Santa Barbara County Health Care Services. Full-time position. Board certified/eligible Occupational Medicine. Clinical and Administrative responsibilities. Send CV to: Gary Erbeck, MPH, Santa Barbara County Health Care Services, 315 Camino del Remedio, Santa Barbara, CA 93110.

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ASSISTANT HEALTH OFFICER—Director of Preventive Medical Services, San Joaquin Local Health District, serving county-wide population of 390,000. Requires: California license; MPH and/or Board quelified in Preventive Medicine, Pediatrics, or Internal Medicine; two years experience in public health. Salary $4,571-$5,555/month, negotiable. Call or write Jack J. Williams, MD, District Health Officer, San Joequin Local Health District, PO Box 2009, Stockton, CA 95201 (209) 466-6781. Equal Employment Opportunity Employer.

GENERAL SURGEON, SUN VALLEY, IDAHO. Energetic general surgeon to practice with multi-specialty group. Well equipped adjacent hospital. Quality of life high, income moderate. Curriculum vitae end references with first letter please. Dr Lynn T. Levy, PO Box 66, Sun Valley, ID 83353.

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FAMILY PRACTICE—Several locations within New Mexico. These are private-practice opportunities with income guarantee. Send CV to Dave Templeton, Southwest Community Health Services, Aubuquerque, NM 87102 or call 1 (800) 545-4030, extension 3050.

PROFESSIONAL PRACTICE SERVICES—Specializing in the sale and appraisal of practices in Sacramento and surrounding Northern Calif. areas. 884 Lincoln Way, Ste. 38, Auburn, CA 95803; (918) 823-2340.

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Résumés should be sent to:

Robin Kubochi
Department of Health Services
Health Protection Division
714 P Street
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Upon receipt of résumé, further information will be provided. The State Department of Health Services is an equal opportunity employer.

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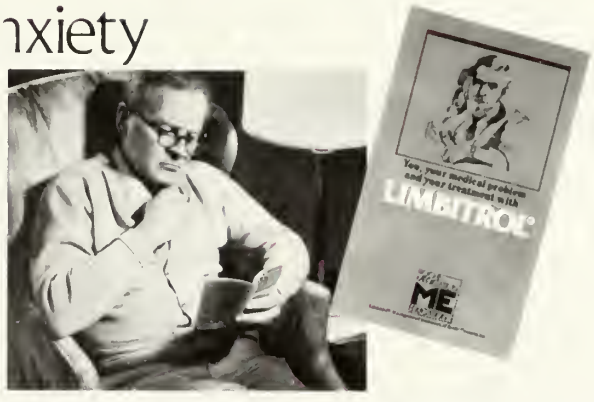
*Feighner JP: *Psychopharmacology* 61 217-225, Mar 22, 1979.



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Warninga: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizera during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studiea. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautiona: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female; elevation and lowering of blood sugar levels; and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500. Tel-E-Dose® packages of 100. Prescription Paks of 50.

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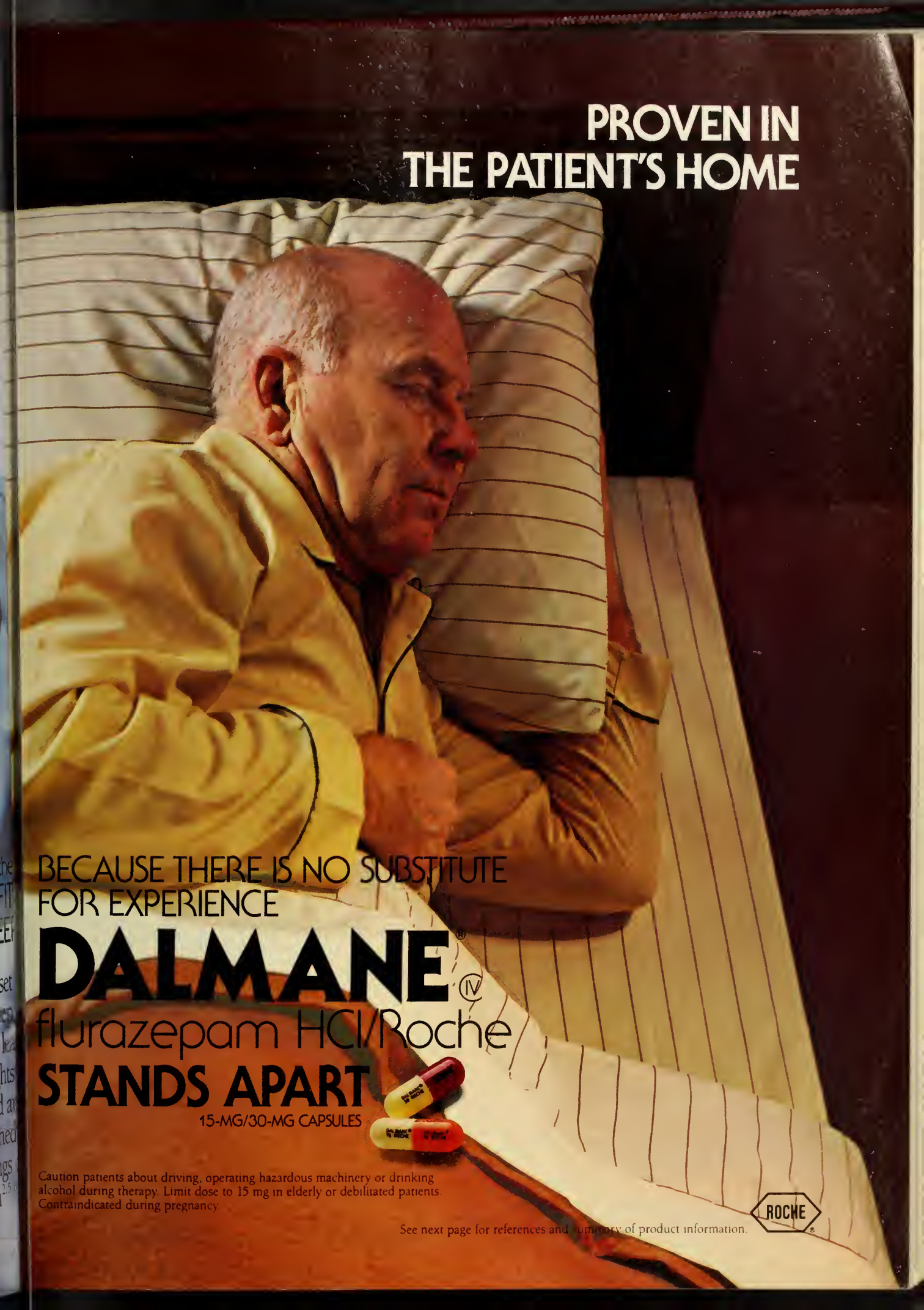
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References: 1. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM. *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res 9*(1):85-99, 1983. **10.** Monti JM: *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep* 5(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage, 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

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(Continued from adjacent page)

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

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Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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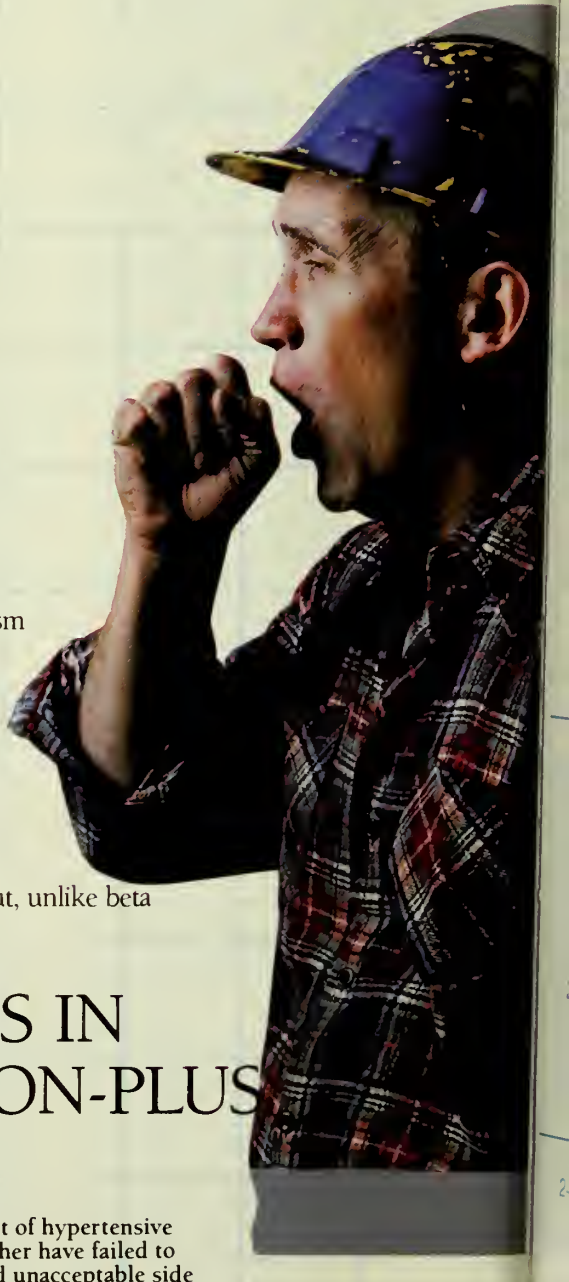

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Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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October 20—**Allergy Update—A Clinical Symposium.** Allergy Foundation of Northern California, Allergy Association of Northern California and the California Society of Allergy at Holiday Inn Union Square, San Francisco. Saturday. Contact: Dr. Chester Trossman, 500 E. Remington Dr., Sunnyvale 94087. (408) 730-0812.

October 24-28—**American Association for Clinical Immunology and Allergy Meeting** at San Diego. Wednesday-Sunday. Contact: Howard S. Silber, Exec. Dir., PO Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

October 25-28—**Allergy, Immunology and Infectious Disease.** Symposium Maui, Inc. and Hawaii Chapter American Academy of Family Physicians at Maui Marriott, Kaanapali, Maui. Thursday-Sunday. 18 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., PO Box 10185, Lahaina, Maui, HI 96761. (808) 661-8032.

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August 17-21—**Clinical Neuroanesthesia Conference.** UCSD at InterContinental Hotel, San Diego. Friday-Tuesday. 22 hrs.

August 19-25—**11th Hawaiian Seminar: Clinical Anesthesiology.** California Society of Anesthesiologists at Maui Surf Hotel, Maui. Sunday-Saturday. $350. Contact: Educational Programs Division, California Society of Anesthesiologists, 100 So. Ellsworth Ave., Ste. 806, San Mateo, CA 94401. (415) 348-1407.

September 8-9—**Case Conference.** High Sierra Hotel at South Shore, Lake Tahoe. Saturday-Sunday. $145. Contact: Educational Programs Division, California Society of Anesthesiolo-

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KEY TO ABBREVIATIONS

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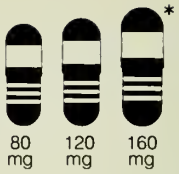
Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirements of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length and diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by fewer anginal episodes and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine- or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the cerebral vessels of the brain.

Beta receptor blockade can be useful in conditions in which beta-adrenergic blockade is therapeutic or functional changes, sympathetic activity is detrimental. This is particularly true in the also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. However, [illegible] drug-related tumorigenic effects at any of the dosage levels. Reproduction studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in rabbit studies at doses about [illegible] greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

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Ayerst AYERST LABORATORIES
New York, N.Y. 10017

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gists, 100 So. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

September 28-30—**Anesthesia Practice 1984.** Anesthesiology Education Foundation at Monterey. Friday-Sunday. 10½ hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles 90024.

October 20—**Annual Anesthesiology Symposium.** Kaiser Permanente Southern California Medical Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

CANCER

October 18-20—**8th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. $300. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

CARDIOLOGY

August 17-19—**Whitewater Raft Conference: Update on Cardiac Drugs and CPR.** Mercy Medical Center at Klamath River. Friday-Sunday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

August 24-26—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress and Holter) and Cardiac Resuscitation.** International Medical Education Corporation at Monterey. Friday-Sunday. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 7-8—**54th Annual Physicians' Postgraduate Symposium on Cardiovascular Diseases.** American Heart Association at San Francisco Hilton Hotel. Friday-Saturday. Contact: Karl Olila, Programs Associate, 421 Powell St., San Francisco 94102. (415) 433-2273.

September 7-9—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Hyatt Islandia, San Diego. Friday-Sunday. Contact: Beverly Jacobsen (800) 525-8651.

September 14-16—**ECG Interpretation, Arrhythmia, and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. 13 hrs. $285. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

September 15-22—**Hawaiian Echocardiography Course.** Institute for Medical Studies at Hawaiian Islands. One week. 20 hrs. $295. Contact: IMS, 14761 Franklin Ave., Ste. A, Tustin 92680. (714) 832-2650.

September 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Meridien Hotel, San Francisco. Thursday-Saturday.

October 7-10—**Cardiology Course**. UCSF at Yosemite. Sunday-Wednesday.

October 11-13—**Cardiology Update—1984.** ACC at Hyatt Del Monte Hotel, Monterey. Thursday-Saturday.

October 15-19—**Pulmonary Medicine Review 1984.** USC. Monday-Friday. $450.

October 26-28—**ECG Interpretation, Arrythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at San Francisco. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 2-4—**The Diagnosis and Management of the Acute Myocardial Infarction.** International Medical Education Corporation at Newporter Inn, Newport Beach. Friday-Sunday. Contact: Beverly Jacobsen. (800) 525-8651.

November 9-10—**Cardiology Update 1984.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. Contact: Lore Kahane, C-SMC, PO Box 4870, Los Angeles 90048. (213) 855-5547.

November 30-December 2—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress & Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 30-December 2—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact Beverly Jacobsen, 64

Inverness Dr. E., Englewood, CO 89112. (800) 525-8651.

EMERGENCY MEDICINE

August 18—**Emergency Medicine Oral Boards Part II.** Highland General Hospital at Hyatt Regency Hotel, Oakland. Saturday. $495. Contact: Robert H. Dailey. (415) 534-8055, Ext. 207.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** American College of Obstetrics and Gynecology at Hotel del Coronado, Coronado. Wednesday-Friday. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 24-26—**Wilderness Emergency Care—Mt. Shasta Summit Expedition.** Mercy Medical Center, Redding at Mt. Shasta. Friday-Sunday. 10 hrs. $350. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 27-31—**Topics in Emergency Medicine.** UCSF at San Francisco. Monday-Friday. $425.

September 1-3—**Whitewater Raft Conference: Wilderness Emergency Care.** Mercy Medical Center at Klamath River. Saturday-Monday. 10 hrs. $295. Contact: Mercy Medical Center, Dept. of Cont. Ed., PO Box 6009, Redding 96099-6009. (916) 243-2121.

September 6-7—**Burns: Emergency and Acute Care.** UCD at Capitol Plaza Holiday Inn, Sacramento. Thursday-Friday.

September 17-21—**Postgraduate Institute for E.R. Physicians, Symposium I.** UCSD at InterContinental Hotel, San Diego. Monday-Friday. 36 hrs.

September 28-29—**Advanced Trauma Life Support Provider Course.** Emergency Shock Trauma Institute, Mercy Hospital at San Diego. Friday-Saturday. 16 hrs. $475. Contact: Emergency Shock Trauma Institute, Mercy Hospital, 4077 5th Ave., San Diego 92103. (619) 294-8111.

October 13—**Emergency Medicine Oral Boards Part II.** Highland General Hospital at Hyatt Regency Hotel, Oakland. Saturday. $495. Contact: Robert H. Dailey. (415) 534-8055, Ext. 207.

October 29-30—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

October 29-November 2—**Intensive Care.** STAN at Rickey's Hyatt, Palo Alto. Monday-Friday.

October 31-November 2—**EMS Today.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 19 hrs.

November 12-16—**Postgraduate Institute for E.R. Physicians, Symposium III.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Friday.

INTERNAL MEDICINE

August 17-19—**2nd Annual La Jolla Summer Conference on Dermatology, Immunology and Rheumatology.** Scripps Clinic and Research Foundation at La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. Contact: Dianne Tisue, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

August 19-24—**New Advances in Internal Medicine.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

September 8—**24th Annual Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Marriott Hotel, Los Angeles. Friday. Contact: National Kidney Foundation of Southern California, 6820 La Tijera Blvd., Ste. 111, Los Angeles 90045. (213) 641-8152.

September 10-15—**6th Comprehensive Nephrology Review Course.** UCLA at Century Plaza Hotel, Los Angeles. Monday-Saturday. 38.5 hrs. $695.

September 15—**Neurology.** UCSF at Fresno. Saturday.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 19—**Common Musculoskeletal Prob-**

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BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM®
(diltiazem HCl)

balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

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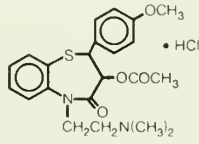
PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-8enzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

Another patient benefit product from

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MARION LABORATORIES, INC
KANSAS CITY, MISSOURI 64137

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★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: The Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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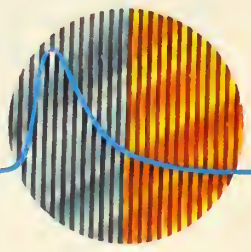
SCIENCE DYNAMICS

IBM

Halcion® 0.25 mg Tablets
triazolam (IV)

Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion
triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

© 1983 The Upjohn Company

Halcion Tablets
triazolam C-IV

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al. Residual effects of hypnotics: triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65

Halcion tablets
triazolam C-IV

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General. In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients. Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests. Not ordinarily required in otherwise healthy patients. Drug Interactions. Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility. No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy. Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers. Administration to nursing mothers is not recommended. Pediatric Use. Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION 1003	Placebo 997
Number of Patients		
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance. HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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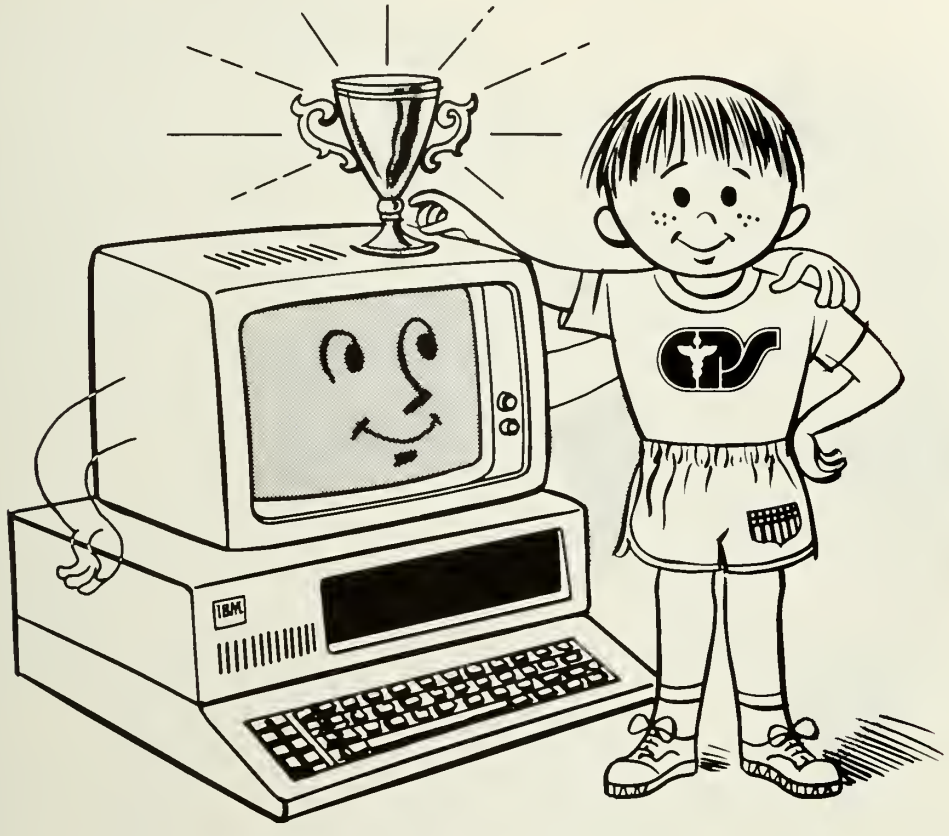

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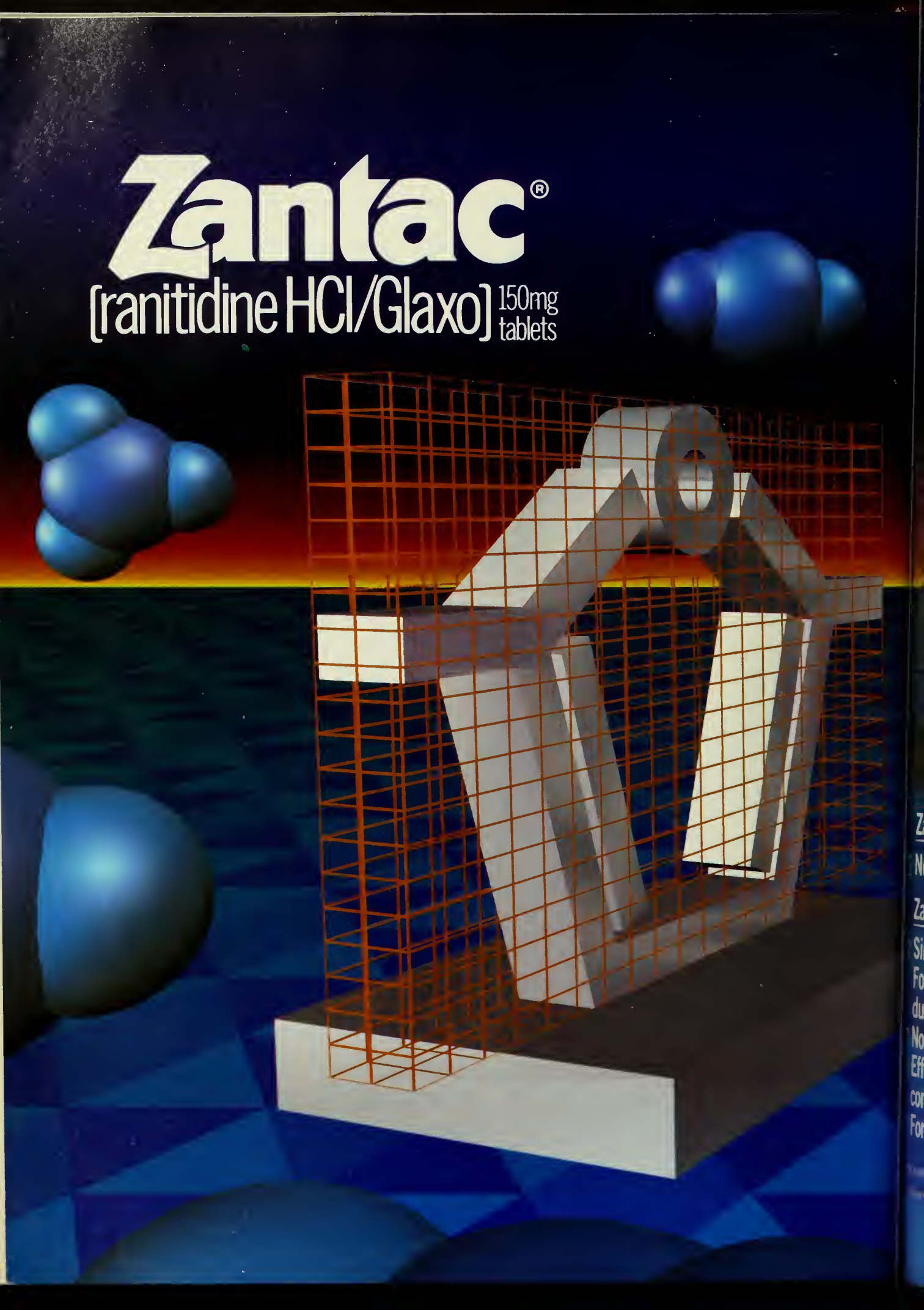
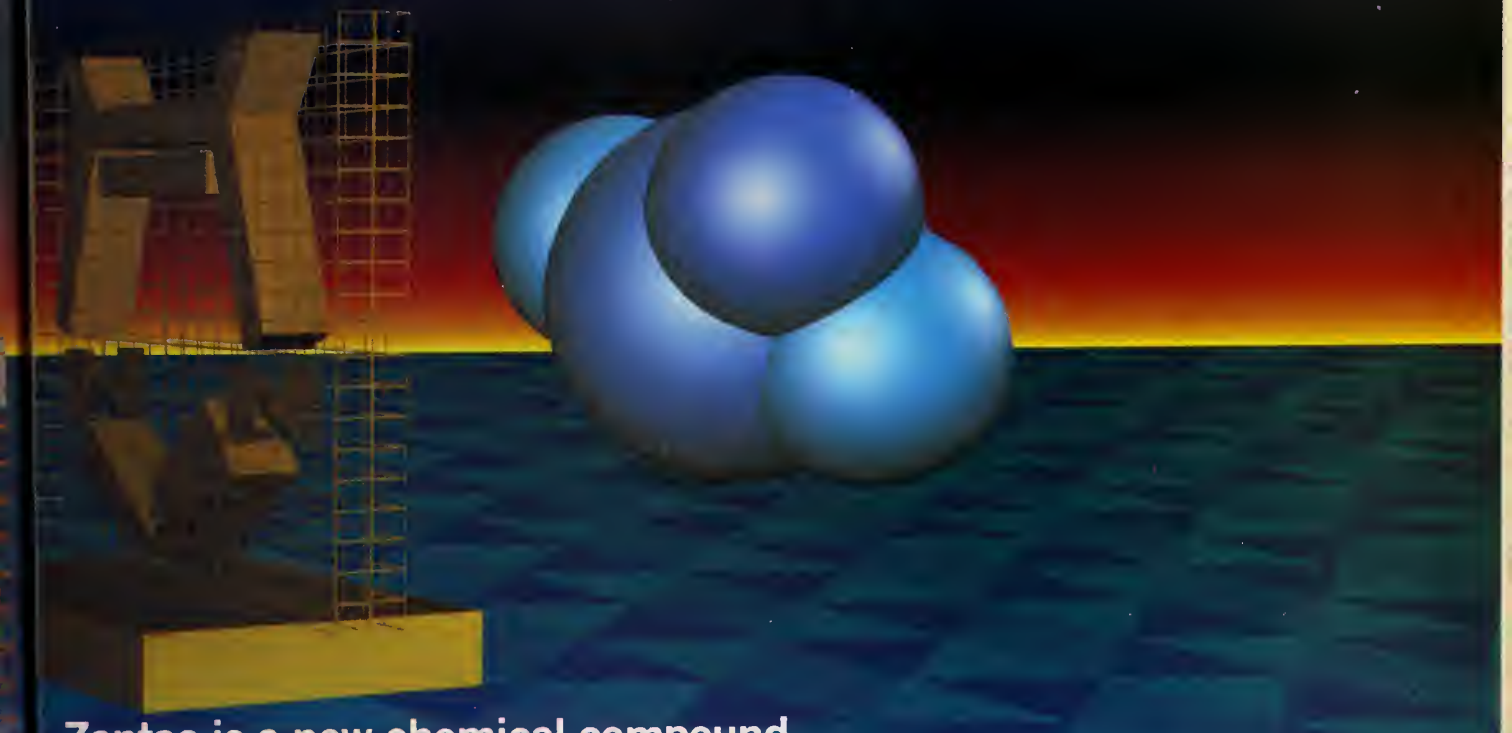
Zantac®

[ranitidine HCl/Glaxo] 150mg tablets



Glaxo ROCHE

Unsurpassed activity in gastric acid inhibition: for active duodenal ulcer and pathological hypersecretory conditions*



Zantac is a new chemical compound

Not a histamine-related imidazole—a furan compound.

Zantac offers important patient benefits

Single-dose action for up to 12 hours—b.i.d. administration.
Four weeks of therapy for most patients with active duodenal ulcer.
No interaction with warfarin, theophylline and diazepam.
Effective and well tolerated even in pathological hypersecretory conditions.
For adverse reactions see complete prescribing information.

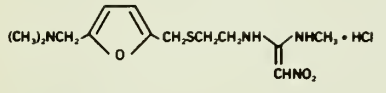
*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers.

Please see following page for complete prescribing information.

Unsurpassed activity in gastric acid inhibition

Zantac®
[ranitidine HCl/Glaxo] 150mg tablets

DESCRIPTION: The active ingredient in ZANTAC® Tablets, ranitidine hydrochloride, is a histamine H_2 receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride. It has the following structure



The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$, representing a molecular weight of 350.87.

Ranitidine hydrochloride is a white to pale yellow granular substance which is soluble in water. It has a slightly bitter taste and sulphur-like odor.

Each tablet for oral administration contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

CLINICAL PHARMACOLOGY: ZANTAC® (rantidine hydrochloride) is a competitive, reversible inhibitor of the action of histamine at the histamine H_2 receptors, including receptors on the gastric cells.

ZANTAC does not lower serum Ca^{++} in hypercalcemic states.

ZANTAC is not an anticholinergic agent.

Antisecretory Activity:

1. **Effects on acid secretion:**
ZANTAC inhibits both daytime and nocturnal basal gastric acid secretion as well as gastric acid secretion stimulated by food, histamine and pentagastrin, as shown in the table below.

Effect of Oral ZANTAC® on Gastric Acid Secretion

	Time After Dose, hrs.	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal, nocturnal and betazole stimulated secretion are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin and food stimulated secretion are more difficult to suppress.

2. **Effects on other gastrointestinal secretions:**
Pepsin: Oral ZANTAC 150 mg did not affect pepsin secretion. Total pepsin output was reduced in proportion to the decrease in volume of gastric juice
Intrinsic factor: Oral ZANTAC 150 mg had no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

3. **Other pharmacological actions:**
a. Hepatic blood flow reduced 20%. Significance unknown.
b. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
c. Prolactin—no effect (IV bolus) or less increase than cimetidine.
d. Other pituitary hormones—no effect on serum gonadotropins, TSH, GH. Possible impairment of vasopressin release.
e. No change in cortisol or aldosterone.
f. No effect on count, motility or morphology of sperm, androgen level, estradiol, testosterone.
g. No effect on penile erection, sexual arousal or ejaculation.

4. **Pharmacokinetics:**
ZANTAC is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440-545 ng/ml occurring at 2-3 hours after a 150 mg dose. The elimination half-life is 2.5-3 hours.

Absorption of ZANTAC is not significantly impaired by concomitant administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36-94 ng/ml. Following a single oral dose of 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 ml/min, indicating active tubular excretion.

In man, the N-oxide is the principal metabolite in the urine; however this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:
Duodenal Ulcer
In a multicenter, double-blind controlled U.S. study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the ZANTAC®-treated patients as shown below:

	ZANTAC® +		Placebo +	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	149	54/147 (37%)*	146	29/137 (21%)
Week 4		109/148 (74%)**		68/137 (50%)

*p = 0.0014
**p = 0.0001
+ All patients were permitted prn antacids for relief of pain.

In these studies, ZANTAC-treated patients reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

	Median number of daily doses of antacid	
	Ulcer Healed	Ulcer Not Healed
ZANTAC®	0.06	0.71
Placebo	0.71	1.43

During the clinical trials, some not healed at 4 weeks were rerandomized to either placebo or ranitidine, with the results after 4 weeks shown below.

Not healed on:	Retreated with:	Healed:
Placebo	Placebo	10/21
Placebo	Ranitidine	15/24
Ranitidine	Ranitidine	5/8
Ranitidine	Placebo	8/19

It can be seen that there are trends weakly favoring ranitidine but none of the differences are statistically significant.

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates. There have been no systematic studies to evaluate whether continued treatment with ZANTAC (ranitidine hydrochloride) alters recurrence rates.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and other pathological hypersecretory conditions (e.g. post-operative, "short gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

INDICATIONS AND USAGE:
ZANTAC® (ranitidine hydrochloride) is indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: There are no known contraindications to the use of ZANTAC® (ranitidine hydrochloride).

PRECAUTIONS:
General
1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see Dosage and Administration). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests
False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interaction
Potentiation of warfarin-type anticoagulants has not been observed with concomitant ZANTAC administration. Likewise no clinically significant drug interactions have been observed between ZANTAC and theophylline or ZANTAC and diazepam. Drug interactions of this type are not expected since ranitidine does not significantly interact with the cytochrome P450 linked drug metabolizing enzyme system.

Carcinogenesis, mutagenesis and impairment of fertility
There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, E. Coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy
Pregnancy Category B. Reproduction studies have been performed in rats and rabits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC® (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
ZANTAC (ranitidine hydrochloride) is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in children have not been established.

Use in Elderly Patients
Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS
Headache has been found to be more frequent in ZANTAC®-treated patients (3%) than placebo-treated patients (2%). The following symptoms have been reported in ZANTAC-treated patients with a frequency of 1% or less: malaise, dizziness, constipation, nausea, abdominal pain and rash.

Decreases in white blood cell and platelet count have occurred in a few patients. These did not lead to cessation of treatment and were clinically insignificant. There have been no reported cases of agranulocytosis or aplastic anemia. Some small increases in serum creatinine have been noted in patients receiving ZANTAC (ranitidine hydrochloride).

Some increases (up to 5 times the upper limit of normal in one case) in serum transaminases and gamma-glutamyl transpeptidase have been reported. Rare cases of hepatitis have been reported.

In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. IV for 5 days. This dose-related effect of the IV formulation suggests that ZANTAC is potentially hepatotoxic. In placebo controlled studies of the oral formulation involving 2437 patients (1358 receiving ranitidine and 1079 patients receiving placebo), with most patients treated 4-8 weeks, there was no difference in incidence of SGOT-SGPT elevations between the 2 groups.

No clinically significant interference with endocrine or gonadal function have been reported.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in animals receiving doses of ZANTAC® in excess of 225 mg/kg/d have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:
Duodenal Ulcer
The current recommended adult oral dosage of ZANTAC® for duodenal ulcer is 150 mg twice daily, the only dose shown to speed healing of duodenal ulcer in U.S. clinical trials. Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in U.S. studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacids given concomitantly and as needed for relief of pain do not interfere with the absorption of ZANTAC.

Since 37% of patients can be expected to show complete healing at the end of two weeks, endoscopy at that time may spare many patients an additional period of treatment.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)
Recommended adult oral dosage: 150 mg twice a day. In some patients it may be necessary to administer ZANTAC 150 mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Dosage adjustment for patients with impaired renal function.
On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED
ZANTAC® Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42), and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening. Manufactured for Glaxo Inc., Research Triangle Park, NC 27709 by Glaxo Operations UK Ltd, Greenford, England.

Issued Sept. 1983

Glaxo
Glaxo Inc., Research Triangle Park, NC 27709

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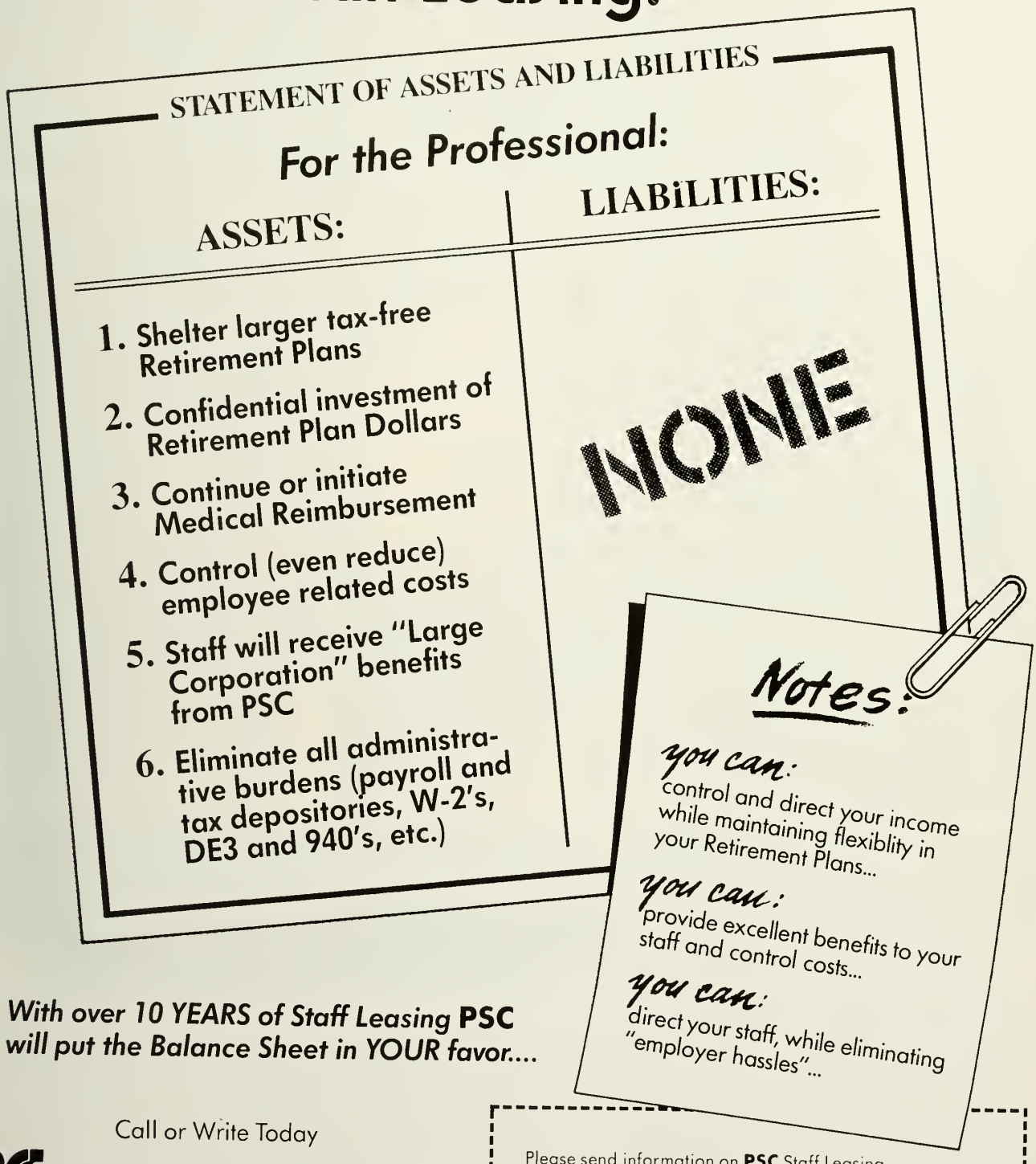
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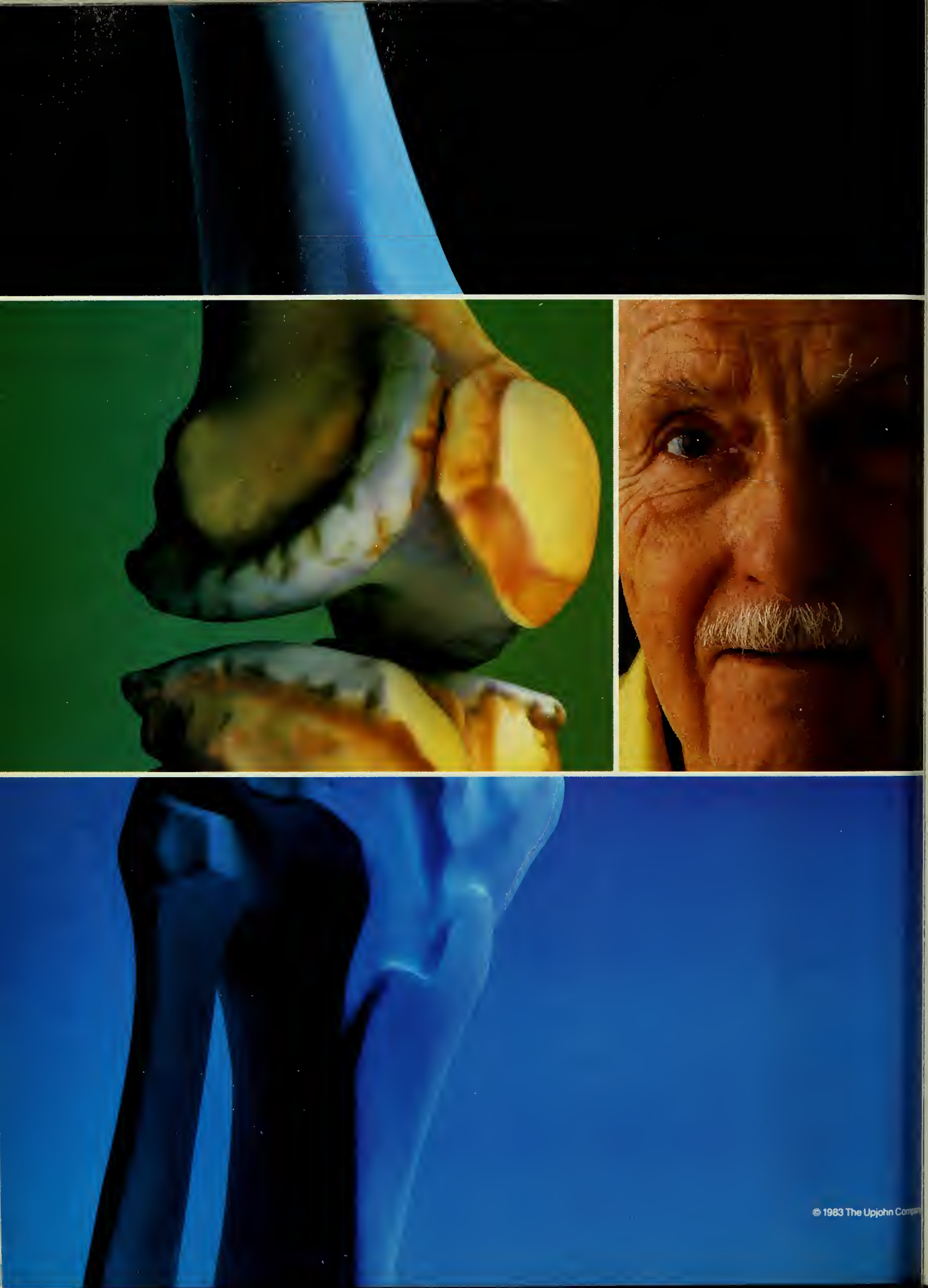

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Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

Advanced age has little or no influence on the pharmacokinetics of *Motrin*.

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

Helping you to help your patients—
Ask your Upjohn Representative for a complimentary supply.

The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS
(ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)–Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%–Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%–Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

Motrin is a registered trademark of The Upjohn Manufacturing Company M. Barceloneta, Puerto Rico

MED B-7-S

Upjohn

(Continued from Page 164)

lems. Veterans Administration Medical Center, Sepulveda. Wednesday. Contact: Charles R. Beeson, MD, Assoc. Chief of Staff for Ed., VA Medical Center, 16111 Plummer St., Sepulveda 91343. (818) 891-2374.

September 19—**Controversial Problems of the Pancreas.** Cedars-Sinai Medical Center at Los Angeles. Wednesday. Contact: Lore Kahane, Cedars-Sinai Medical Center, PO Box 48750, Room 2049, Los Angeles 90048. (213) 855-5547.

September 21-22—**29th Annual Internal Medicine Symposium.** Kaiser Permanente Southern California Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. $150. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 1-5—**Present Concepts in Internal Medicine.** American College of Physicians at San Francisco. Monday-Friday. Contact: ACP Headquarters, (215) 243-1200.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** See Allergy and Immunology, October 15-18.

October 17—**Diabetes—1984.** The Hospital of the Good Samaritan at Hyatt Regency Hotel Los Angeles, Los Angeles. Wednesday. Contact: Dolores Gay, Coordinator of Symposia, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

October 19-21—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** Continuing Medical Education Associates at Vacation Village Hotel, San Diego. Friday-Sunday. Contact: Jackie Shiller, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

November 2-3—**Thyroid/Diabetes Workshop.** UCSF. Friday-Saturday.

November 2-4—**Practical Endocrinology: Workshop in Thyroid and Diabetes.** UCSF at Claremont Resort Hotel, Berkeley. Friday-Sunday. Reg. Info.: 666-5808. Program Info.: 666-4251.

November 10—**Infectious Disease.** UCD at Holiday Inn Holidome, Sacramento. Saturday.

November 10—**Pulmonary Medicine.** UCSF at

(Continued on Page 268)

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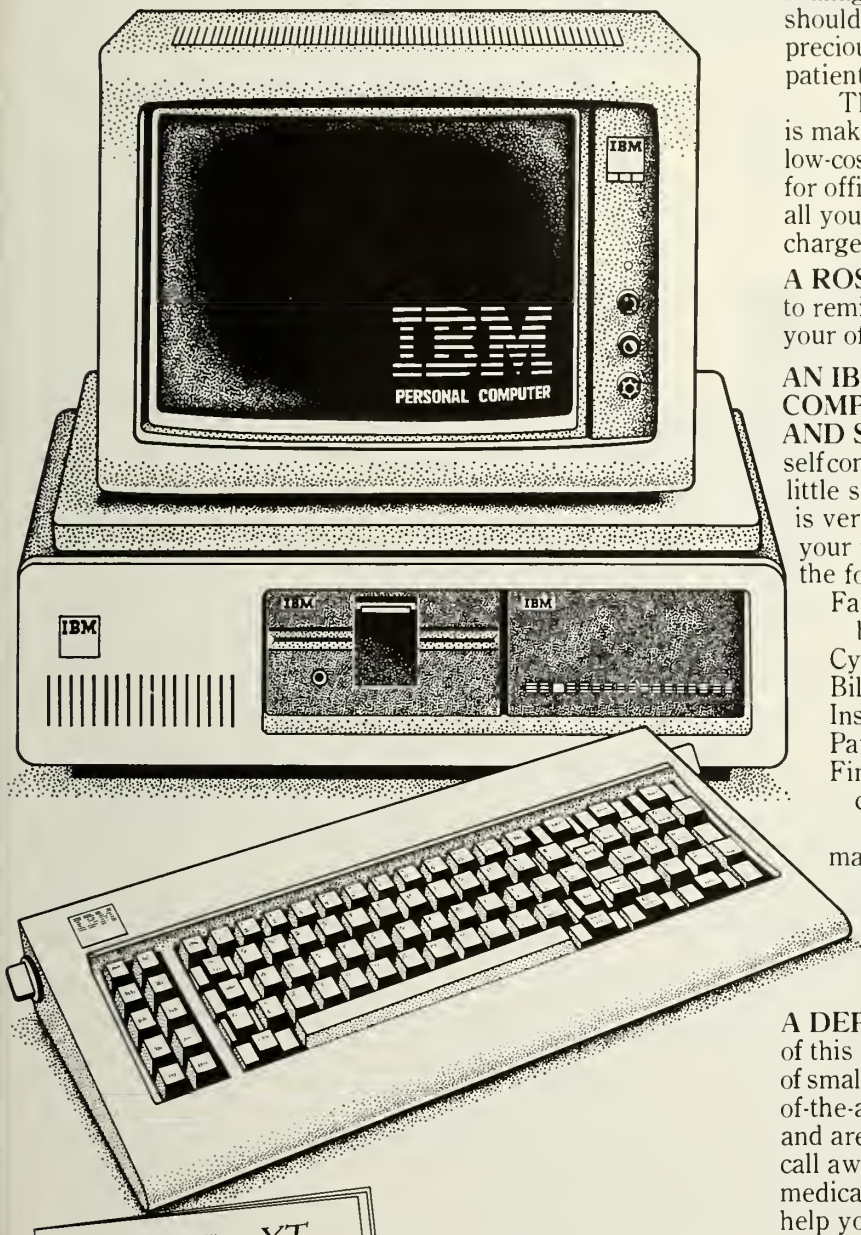

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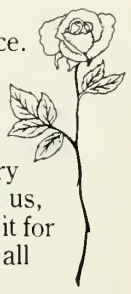

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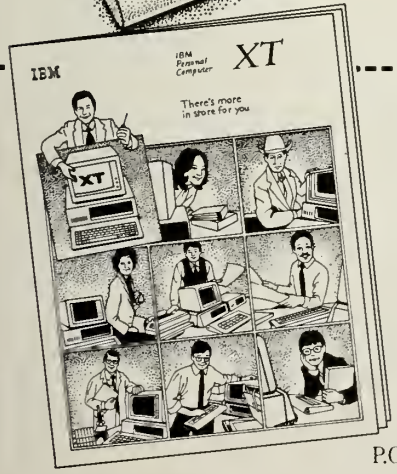

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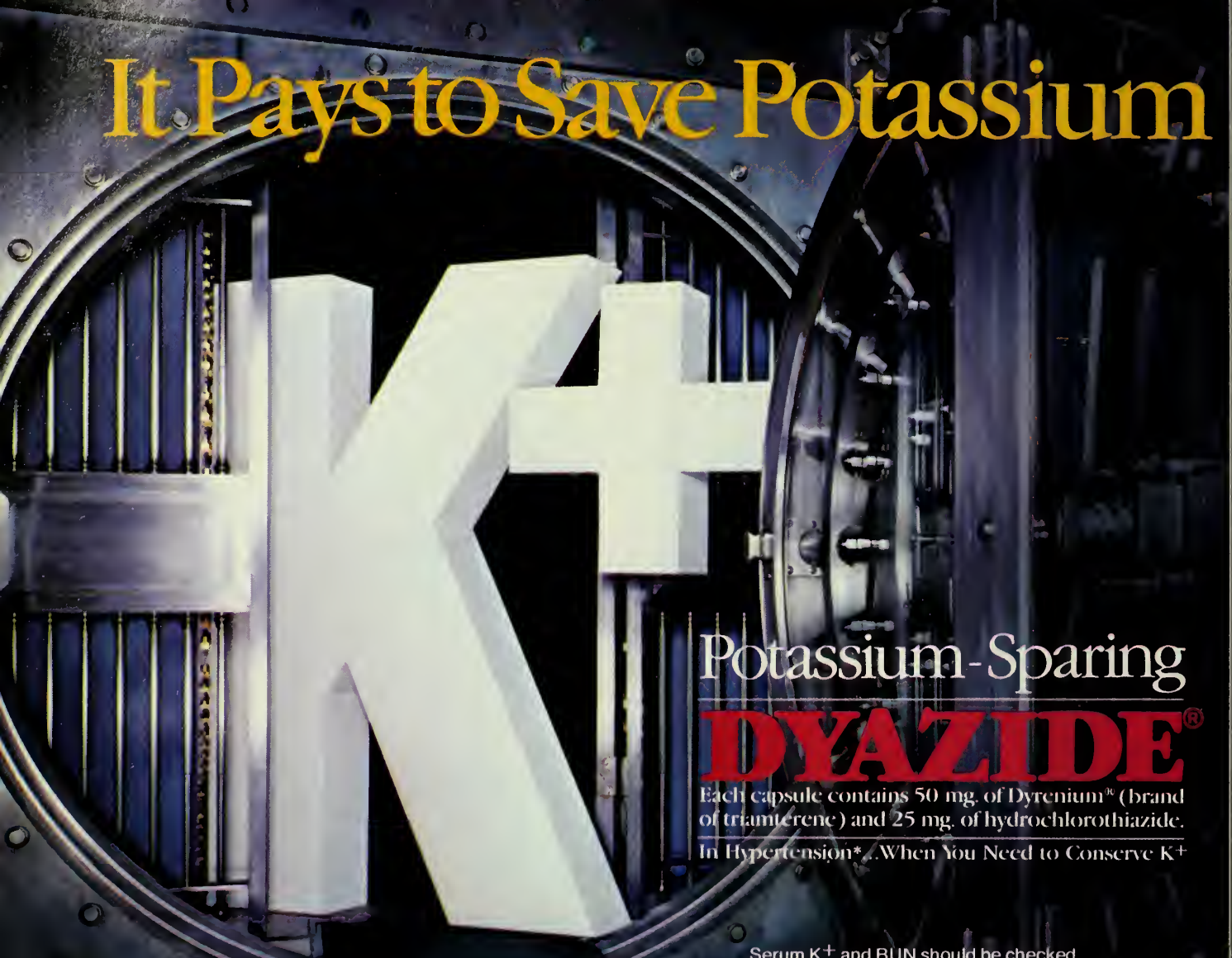
It Pays to Save Potassium



Potassium-Sparing

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

In Hypertension*...When You Need to Conserve K^+

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); In Patient-Pak™ unit-of-use bottles of 100.

The unique red and white Dyazide® capsule: Your assurance of SK&F quality

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Clinical Investigation

Health Status of Southeast Asian Refugees

FRANKLYN N. JUDSON, MD; DEBORAH M. LINCE, MD; BRONWEN J. ANDERS, MD; JANET M. TAPY, RN; DAVID LE VAN; DAVID L. COHN, MD, *and* TAMARA J. KICERA, *Denver*

The rates of several diseases have been reported to be higher among Southeast Asian refugees compared with those of indigenous North Americans. When we prospectively evaluated 991 refugees new to the Denver metropolitan area for their health and immunization status over a 12-month period, 38% were found to be tuberculin-positive, 71% carried one or more enteric parasites, 15% were HBsAg-positive, 13% had anemia and 31% either presented without immunization records or required continuation of vaccination sequences begun in overseas camps. Age and ethnicity were important variables with regard to tuberculosis, hepatitis B and anemia. The rates of specific parasitic infestations varied among the four ethnic groups, though the overall rates of parasitosis remained constant across ethnic lines.

(Judson FN, Lince DM, Anders BJ, et al: Health status of Southeast Asian refugees [Clinical Investigation]. West J Med 1984 Aug; 141:183-188)

Since 1975, more than 600,000 Indochinese refugees have entered the United States.[1] Immediately following the fall of the South Vietnam government, the majority of refugees were Vietnamese—often well-educated city dwellers. As the ensuing social upheaval penetrated more of Indochina, rural Vietnamese, Laotians and Cambodians also fled their countries. Many of the later refugees had had little experience with Western life-styles, particularly with Western medicine.

By November 1982, Colorado had received 10,548 Southeast Asian refugees,[1] most of whom settled in the City and County of Denver and the five surrounding counties. In view of the scarcity of modern sanitation and health facilities in Southeast Asia, we anticipated that rates of tuberculosis, enteric parasites and hepatitis B infection would be much higher among refugees than among indigenous North Americans. To better meet the public health and medical needs of refugees, Denver Disease Control (DDC), with support from the Colorado Department of Health, initiated in May 1981 a comprehensive health screening program. It was designed to screen refugees soon after they arrived from Southeast Asia for tuberculosis, intestinal parasites, hepatitis B infection, anemia and immunization status and to introduce them to an appropriate health care system.

In previous studies disease prevalence rates among this population have been investigated. Catanzaro and Moser noted a tuberculin skin test positivity rate of 55% among Southeast Asian refugees in San Diego,[2] whereas the Centers for Disease Control (CDC) reported that 41% of refugees younger than 18 years of age and living in San Francisco had positive tuberculin tests.[3] The age-specific incidence rates of bacteriologically confirmed tuberculosis are 14 to 70 times higher than for the United States population as a whole.[4] Wiesenthal and co-workers found that 78% of 165 Meo (Hmong) Laotians harbored at least one enteric parasite.[5] In a Mayo Clinic study, of 100 Southeast Asian patients screened, 43% had multiple intestinal parasites.[6] Among immigrants to New Mexico, 72% had intestinal parasites including 44% with multiple infestations.[7]

Malaria by contrast has been detected infrequently in asymptomatic persons. No positive smears were detected in 407 Southeast Asians prospectively screened in San Diego.[2] Tittle and associates examined 100 Southeast Asian children for infectious diseases and found three cases of clinically apparent malaria. As no asymptomatic child had a positive smear, they discontinued routine malaria screening.[8]

Variations in prevalence rates of these diseases have

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ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette Guérin
CDC = Centers for Disease Control
DDC = Denver Disease Control
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
PPD = purified protein derivative
PVA = polyvinyl alcohol

been attributed to age, socioeconomic and ethnic differences. Indeed, the Southeast Asian population includes at least four important ethnic groups with very different cultural and epidemiologic risk factors. The purpose of our study is to describe the Colorado comprehensive Southeast Asian refugee screening program and to determine, prospectively, disease prevalence rates by age and ethnicity.

Methods

Refugees arriving directly from Southeast Asia were identified by notifications to the Colorado Department of Health from the US Immigration and Naturalization Service, the US Quarantine Service, voluntary agencies and refugee social service centers. The Colorado Department of Health in turn provided monthly listings to DDC (Denver Public Health, Denver Department of Health and Hospitals). Refugees arriving in Colorado after variable periods of established residency in other states were examined, but those results are not included in this study.

The DDC sent letters to both refugee and sponsor requesting that each refugee appear for health screening. On arrival at the DDC, each refugee was interviewed by one of two multilingual workers, one of whom was fluent in Vietnamese, Laotian, Cambodian, Thai, French and English and the other in Vietnamese and English.

For a 12-month period from July 1, 1981, through June 30, 1982, we attempted to screen each refugee for tuberculosis, enteric parasites, hepatitis B virus infection, anemia and immunization status. Not all screening procedures were completed on all patients owing to refused venipuncture or missed follow-up visits—that is, failure to return for skin test reading or with stool specimens. Malaria screening was not carried out in asymptomatic refugees.

Tuberculosis Screening

Each tuberculosis skin test was done by an experienced nurse using a 0.1-ml intracutaneous injection of 5 tuberculin units of stabilized tuberculin purified protein derivative (PPD) (Tubersol, Squibb/Connaught, Inc, or Aplisol, Parke-Davis). Skin test reactions were interpreted after 48 to 72 hours, a transverse induration of 10 mm being considered positive. Refugees with a 5- to 9-mm reaction were tested again.

Posteroanterior x-ray films of the chest were done on positive PPD reactors and read by clinic physicians. Sputum specimens were obtained from patients with positive skin tests who had either symptoms (weight loss, cough, hemoptysis or night sweats) or abnormalities on a chest x-ray film. Each of three morning specimens was concentrated, stained with auramine O and cultured on 7-H-11 biplates (Pasco Laboratories, Wheat Ridge, Colo), which were examined at three and six weeks following inoculation.

In addition to those persons found by our screening program to have active tuberculosis, some refugees were labeled class A (chest x-ray findings thought to be consistent with active pulmonary tuberculosis) by the US Public Health Service before their arrival in Colorado and were already being treated. Therapy for active tuberculosis was initiated, continued or modified by a staff clinician. Patients with positive tuberculin skin tests and normal chest x-ray examinations (class 2) or findings on x-ray film of chest consistent with inactive disease (class 4) were offered isoniazid preventive therapy for one year.[9]*

Enteric Parasite Screening

Each refugee was asked to put stool specimens in two containers (polyvinyl alcohol [PVA] and formalin). The specimens were processed by the Colorado Department of Health's Parasitology Laboratory. The PVA specimen was stained with trichrome and examined for *Giardia lamblia* and amebae. The formalin specimen was examined by direct microscopy, ether sedimentation and zinc sulfate flotation. Refugees with parasites were contacted by telephone or letter by our multilingual health workers and asked to return for treatment.

Hepatitis B Screening

Blood specimens from refugees 15 years of age or older were tested for hepatitis B surface antigen (HBsAg; Ausria II, Abbott Laboratories, North Chicago, Ill) by the Hepatitis Laboratories Division, Centers for Disease Control, Phoenix. We sent letters to Denver's Neighborhood Health Centers, the Denver General Hospital and the University Hospital's Obstetrics Clinics, alerting clinicians to the high prevalence of hepatitis B infections in Southeast Asian women and informing them that test results were available from the patients or through DDC.

Anemia Screening

Hematocrits were measured by Denver Disease Control using a fingertip puncture method (Monolet lancets, Sherwood Medical, St Louis, Mo) with heparinized capillary tubes (Red Tips, Fisher Scientific, Pittsburgh). Anemia was defined by the following age- and sex-adjusted scale: less than 38% for women older than 15 years, less than 42% for men older than 15 years and less than 35% for children 15 years or younger.

*Classes A and B are Public Health Service classifications of tuberculosis in refugees: class A is active tuberculosis as determined by chest x-ray findings; class B is old, inactive tuberculosis. Classes 1 through 5 are the American Thoracic Society's classification.

Refugees with anemia were referred to an appropriate clinic for evaluation and treatment.

Immunization Status

Most refugees presented with an immunization card from the Intergovernmental Committee for Migration, which was reviewed by a health worker. An adequate immunization status was determined by the Recommendations of the Immunization Practices Advisory Committee of the Centers for Disease Control.[10] Inadequately immunized refugees were appropriately immunized. Refugees without records were treated as if they had had no previous immunizations.

Results

About 95% of all refugees who came to the Denver metropolitan area directly from Southeast Asia between July 1, 1981, and June 30, 1982, were screened. Table 1 presents demographic data by ethnic group, age and sex for these 991 refugees. Vietnamese constituted more than half (58%), followed by Cambodians (26%), Laotians (12%) and Hmong (5%). There were more male (60%) than female (40%) Vietnamese, but sex disparities were less evident for the other ethnic groups. Most refugees were young; median age was 25 years.

TABLE 1.—*Age and Sex Characteristics by Ethnic Group of 991 Southeast Asian Refugees Screened by Denver Disease Control, July 1, 1981, Through June 30, 1982*

	Ethnic Group			
Characteristics	Vietnamese N=571 Number (Percent)	Cambodian N=254 Number (Percent)	Laotian N=120 Number (Percent)	Hmong N=46 Number (Percent)
Sex				
Male	345(60.4)	118(46.5)	54(45.0)	24(52.2)
Female ..	226(39.6)	136(53.5)	66(55.0)	22(47.8)
Age (years)				
0-19	328(57.4)	139(54.7)	73(60.8)	30(65.2)
20-39	221(38.7)	96(37.8)	27(22.5)	9(19.6)
40-59	18(3.2)	14(5.5)	14(11.7)	3(6.5)
60+	4(0.7)	5(2.0)	6(5.0)	4(8.7)

TABLE 2.—*Rates of Infection with Mycobacterium tuberculosis by Ethnicity and Age in 923 Southeast Asian Refugees, Denver Disease Control, July 1, 1981, Through June 30, 1982*

		Purified Protein Derivative Skin Test Positive			
		Chest X-ray Findings Negative		Chest X-ray Findings Positive*	
Group	Number Tested	Number	(Percent)	Number	(Percent)
Ethnicity					
Vietnamese ...	535	203	(37.9)	11	(2.1)
Cambodian ...	230	101	(43.9)	15	(6.5)
Laotian	110	20	(18.2)	0	(0.0)
Hmong	46	1	(2.2)	2	(4.3)
Age (years)					
0-19	526	135	(25.7)	9	(1.7)
20-39	342	159	(46.5)	13	(3.8)
40-59	37	24	(64.9)	1	(2.7)
60+	18	7	(38.9)	5	(27.8)
TOTAL	921†	325	(35.2)	28	(3.0)

*Chest X-ray Finding Positive = consistent with tuberculous infection, past or current.
†Ethnicity could not be determined in two refugees.

Tuberculosis Screening

Of 923 patients skin tested (Table 2), 353 (38%) had positive reactions including 28 (3%) with chest x-ray findings consistent with past or current tuberculous infection. The highest rate of tuberculin positivity by ethnic group was found in Cambodians (50%), who also had the highest rate of abnormalities seen on chest x-ray examination (7%). The highest rate of tuberculin positivity by age was in 40- to 59-year-olds (68%), followed by 20- to 39-year-olds (50%). In addition, 19 cases of active tuberculosis were diagnosed, including 11 with class A tuberculosis that had been identified and chemotherapy begun while the patients were in refugee camps. The eight cases of tuberculosis detected by our screening program comprised children or young adults with hilar lymphadenopathy or upper lobe infiltrates on chest roentgenogram without bacteriologic confirmation, and one adult who had tuberculous arthritis of the knee.

Intestinal Parasites

Of 781 refugees who provided stool specimens for examination (Table 3), 71% had at least one parasite and 39% more than one. Most frequent were hookworm (42%), *Trichuris trichiura* (26%) and *Ascaris lumbricoides* (18%).

In Vietnamese, hookworm, *Trichuris* and *Ascaris* infestations were found in 33%, 39% and 27%, respectively, whereas in Cambodians, Laotians and Hmong, hookworm was more common (56%, 51% and 67%, respectively) and *Trichuris* much less common (8%, 16% and 4%). *Clonorchis sinensis* was found in 20% of Laotians, but in less than 5% of Cambodians and in only one Vietnamese. Infestation rates varied little with age, except in the group older than 60 years, in which rates were lower (Table 4).

Hepatitis B Screening

HBsAg was tested for in 516 refugees 15 years of age and older (Table 5). Overall, 15% were positive: 30 (13%) women and 46 (16%) men. The prevalence of antigenemia decreased with increasing age. Rates varied by ethnic group: Vietnamese, 20%, Cambodians, 16%, and Laotians, 11%.

Anemia Screening

Hematocrits were done on 746 refugees, of whom 95 (13%) were anemic, including 42% of Hmong, 20% of Cambodians, 10% of Vietnamese and 5% of Laotians.

Immunization Status

Of 852 refugees whose immunization status was reviewed, 267 (31%) either presented without immunization records or required continuation of vaccine sequences begun in overseas camps (44% of Hmong,

41% of Laotians, 30% of Cambodians and 28% of Vietnamese).

Discussion

Our prospective active screening program enabled us to screen about 95% of refugees who came directly from Southeast Asia to the Denver metropolitan area between July 1, 1981, and June 30, 1982. This method avoided most possibilities for selection bias. By contrast, some previous studies have assessed the health status of refugees who presented to medical clinics, which may have selected for a subset less representative of the overall refugee population.[6,8]

Children and young adults predominated in this study population (82% were younger than 30 years; median age was 15 years), which typifies the demographics of their countries of origin. Median age is low owing to higher birth rates and decreased life expectancy.[11]

With such a young population, the opportunity for effective preventive health measures is great. For example, 146 refugees younger than 20 years of age were found to have positive PPD reactions. Children younger than 5 years and adolescents have a higher risk of breakdown to active tuberculosis; the British Medical Research Council reported that in 8.1% of adolescents who had positive skin tests, active pulmonary tuberculosis developed within ten years of primary infection.[12] Barnett and Styblo reported a 9% breakdown rate in 15- to 25-year-old skin-test-positive Canadians who were observed for 12 years.[13]

TABLE 5.—*Rates of Hepatitis B Virus Carriage (Positive for Hepatitis B Surface Antigen) by Ethnic and Age Groups in 283 Male and 233 Female Southeast Asian Refugees Screened by Denver Disease Control, July 1, 1981, Through June 30, 1982*

Group	Men			Women		
	Number Tested	Number Positive	(Percent)	Number Tested	Number Positive	(Percent)
Ethnicity						
Vietnamese	174	28	(16.1)	120	21	(17.5)
Cambodian	68	12	(17.6)	70	7	(10.0)
Laotian	41	6	(14.6)	43	2	(4.7)
Age (years)						
15-19	46	7	(15.2)	26	5	(19.2)
20-39	202	36	(17.8)	168	21	(12.5)
40-59	27	3	(11.1)	24	2	(8.3)
60+	8	0	(0.0)	15	2	(13.3)

Both a positive tuberculin reaction and abnormalities on a chest roentgenogram were found in 3% of refugees. A study of rural Europeans older than 35 years who had this combination showed that each year 1% to 2% had reactivation of pulmonary tuberculosis.[14] In black Americans of lower socioeconomic status, the reactivation rate was higher—6% per year.[15] Although the Public Health Service notified us of 11 cases of active tuberculosis, an additional 8 active cases were identified by our screening program. Detecting these persons soon after they arrive in the United States should prevent development of more exensive disease and spread to close contacts.

Our overall prevalence of tuberculin positivity of 38% is similar to the 41% rate reported for San

TABLE 3.—*Parasite Infestation Rates by Ethnic Group in 781 Southeast Asian Refugees, Denver Disease Control, July 1, 1981, Through June 30, 1982**

Parasite	Ethnic Group							
	Vietnamese (N=446)		Cambodian (N=212)		Laotian (N=96)		Hmong (N=27)	
	Number	(Percent)	Number	(Percent)	Number	(Percent)	Number	(Percent)
Hookworm	146	(32.7)	118	(55.7)	49	(51.0)	18	(66.7)
Trichuris trichiura	172	(38.6)	16	(7.5)	15	(15.6)	1	(3.7)
Ascaris lumbricoides	121	(27.1)	11	(5.2)	4	(4.2)	5	(18.5)
Strongyloides stercoralis	29	(6.5)	52	(24.5)	7	(7.3)	2	(7.4)
Giardia lamblia	34	(7.6)	20	(9.4)	11	(11.5)	4	(14.8)
Clonorchis sinensis	1	(0.2)	10	(4.7)	19	(19.8)	0	(0.0)
Hymenolepis nana	0	(0.0)	15	(7.1)	2	(2.1)	0	(0.0)
Entamoeba histolytica	8	(1.8)	3	(1.4)	1	(1.0)	1	(3.7)

*Almost 40% had more than one parasite.

TABLE 4.—*Parasite Infestation Rates by Age in 781 Southeast Asian Refugees, Denver Disease Control, July 1, 1981, Through June 30, 1982*

Parasite	Age Group (Years)							
	0-19 (N=450)		20-39 (N=280)		40-59 (N=36)		60+ (N=15)	
	Number	(Percent)	Number	(Percent)	Number	(Percent)	Number	(Percent)
Hookworm	170	(37.8)	138	(49.3)	17	(47.2)	6	(40.0)
Trichuris trichiura	120	(26.7)	75	(26.8)	7	(19.4)	2	(13.3)
Ascaris lumbricoides	84	(18.7)	53	(18.9)	5	(13.9)	0	(0.0)
Strongyloides stercoralis	45	(10.0)	41	(14.6)	3	(8.3)	1	(6.7)
Giardia lamblia	49	(10.9)	17	(6.1)	2	(5.6)	1	(6.7)
Clonorchis sinensis	15	(3.3)	8	(2.9)	6	(16.7)	1	(6.7)
Hymenolepis nana	12	(2.7)	5	(1.8)	0	(0.0)	0	(0.0)
Entamoeba histolytica	9	(2.0)	4	(1.4)	0	(0.0)	0	(0.0)

Francisco area refugees.[3] The four ethnic groups had very different rates of tuberculous infection: 50% of Cambodians had positive tuberculin reactions compared with 39% of Vietnamese, 18% of Laotians and 7% of Hmong. Catanzaro and Moser also noted ethnic differences but in their study 69% of Vietnamese, 57% of Cambodians, 48% of Laotians and 15% of Hmong were positive.[2] The use of bacille Calmette Guérin (BCG) vaccination in these individual countries and hence the relative contribution of this vaccine to tuberculin-positivity rates is unknown.

Two issues should be addressed with regard to our skin testing: (1) the use of Aplisol tuberculin and (2) the previously reported high rate of PPD conversion among Southeast Asians. Blackshear and colleagues reported a high rate of false-positive skin tests with the use of Aplisol as compared with Tubersol.[16] Nevertheless, the CDC has recommended against repeating skin tests in Southeast Asian refugees because of their high risk of having tuberculosis (Centers for Disease Control, written communication, September 1982). Though about half of our patients were tested with Aplisol, our rates are similar to those of published studies in which Tubersol was used.[2,3]

At Monroe County Health Department in New York, 43% of 217 refugees with negative skin tests had positive results on retesting.[17] It is currently unknown if this phenomenon is related to boosting of remote *Mycobacterium tuberculosis* infection, recent tuberculous infection occurring before immigration, previous BCG vaccination, changes in nutrition or other factors. The CDC has recommended that retesting of Southeast Asian reactors not be done routinely if the initial test result is negative.[18] In our program we retested only those persons with doubtful (5 to 9 mm) reactions.

Almost 75% of our refugee population had one or more enteric parasites. Although Colorado's dry northern climate and relatively safe water supplies preclude any public health risk from these infestations, persons may suffer without treatment. Hookworm infestation, for example, may be heavy enough to produce an iron deficiency anemia,[19] an association found in the San Diego refugees.[2] We were unable to consistently document this expected relationship by comparing rates within and between ethnic groups. Hmong, for example, had the highest rates of both hookworm (67%) and anemia (42%) whereas 51% of Loatians had hookworm but only 5% were anemic.

Strongyloides stercoralis infested 12% of refugees. Although most infested persons will be asymptomatic or have only moderate symptoms of enteritis, *Strongyloides* can "autoinfect" its host, allowing prolonged infestation. Moreover, old age, debilitating disease or immunosuppressive therapy can permit development of a hyperinfection syndrome in which the parasite disseminates throughout the body.[20,21] At the University of Kentucky, disseminated disease developed in 1.5% to 2.5% of patients who had strongyloidiasis.[20]

HBsAg was found in 15% of adult refugees, a rate similar to the 14% reported from San Diego[2] and to rates reported by the CDC.[22] Hepatitis B virus (HBV) can cause acute hepatitis, chronic active hepatitis, cirrhosis and hepatocellular carcinoma. Sexual partners of HBsAg carriers, newborns and other children of carrier mothers and dental and medical personnel working with the HBsAg-positive refugees are at high risk of acquiring hepatitis B. If negative for HBV serologic markers, these persons should be offered hepatitis B vaccine.[23] In a family unit, it may be most practical to offer hepatitis B vaccine to all HBV-seronegative family members who will have continuing close physical contact with an HBsAg carrier.

By measuring hematocrit, we hoped to identify refugees with nutritional deficiencies, hemoglobinopathies, thalassemia or bleeding disorders to refer them for further medical evaluation. Hmong (42%) and Cambodians (20%) were most likely to have anemia. Catanzaro and Moser detected lower hemoglobin levels among Cambodians and Laotians compared with Hmong and Vietnamese.[2] Cambodians may have a higher prevalence of anemia because of greater socioeconomic disruption or higher rates of thalassemia and hemoglobinopathies.

Although overseas refugee camps attempt to immunize incoming refugees, our results imply that these efforts have not completely succeeded: a third of our study population required further immunizations. Determination of immunization status, however, depended on review of a refugee camp immunization card that refugees were asked to bring to clinic. It is likely that some refugees whose immunizations were up-to-date had no card upon evaluation at the DDC, falsely elevating our calculated rates.

The immunization status of Americans of all ages has not been studied. In 1982 the Colorado Department of Health did an immunization survey of 276 2-year-old children and found 71% had completed the recommended immunization schedule (three or more diphtheria and tetanus toxoids and pertussis vaccine; three or more oral poliovirus vaccine, and one measles, mumps and rubella virus vaccine).[24] By October of their first year in school, however, 95% of Colorado children were completely immunized. Although Southeast Asians may be fully immunized less often than indigenous Coloradoans, this gap should be easily closed. The public health and preventive medicine goals of fully immunizing at least 95% of the population remain clear-cut.

We conclude that Southeast Asian refugees on arriving in the United States are far more likely than indigenous Americans to have enteric parasites, infections with *M tuberculosis* and HBV, anemia and a suboptimal immunization status. Our findings emphasize the heterogeneity of this population with regard to rates of specific diseases.

A program such as ours helps to more completely and efficiently screen refugees to permit early eradication of enteric parasites, treatment and prevention of *M tuberculosis* infections, prevention of HBV infections, evaluation and treatment of anemia and preven-

tion of other communicable diseases through immunizations. The program also serves to familiarize refugees with many aspects of modern preventive medicine and to refer them to appropriate long-term health care providers. Copies of screening results held by both the DDC and the refugee or guardian should reduce the likelihood that unnecessary diagnostic tests, treatment and immunizations will be done at a later date.

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Differences Between Right and Left Arm Blood Pressures in the Elderly

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Recommendations vary on whether blood pressures should be measured in the right or in the left arm because no frequency distributions for a pressure difference between the arms exist. We took a total of 12 blood pressure determinations in both arms of 174 elderly persons and analyzed the data by a least-squares components of variance method. The mean difference between the arms (right minus left) was 0.93 mm of mercury for systole and 0.70 mm of mercury for diastole. For systole the proportion of persons having arm pressure differences exceeding 10 mm of mercury is 1.4% and that exceeding 7.5 mm of mercury is 6.5%. For most people, the pressure difference between the arms is small.

(Hashimoto F, Hunt WC, Hardy L: Differences between right and left arm blood pressures in the elderly [Clinical Investigation]. West J Med 1984 Aug; 141:189-192)

When routine blood pressure measuring became standard office practice almost half a century ago, discrepancies between the pressures of the right and left arms were noted.[1] Since then, there has been no consensus on whether significant differences do, or even might, exist. The American Heart Association stated that on the initial examination, blood pressures should be determined in both arms and thereafter pressures should be followed on the side that initially had the highest pressure.[2] Recently, however, in large population blood pressure studies, the arm that was tested was not specified[3] or the pressures were taken only on the right side.[4] A study of different sphygmomanometers that were candidates for use in the Hypertension Detection and Follow-up program did not consider arm or order effects when taking the comparative blood pressure measurements.[5] That no consensus on the issue of blood pressure differences between the arms exists is not surprising because the needed information, distributions of blood pressure discrepancies between the two arms, has not been heretofore available.

We used an electronic sphygmomanometer, which eliminated observer and recorder biases inherent in using the traditional mercury apparatus, and took multiple pressure readings in both arms of many persons. Using a least-squares components of variance method, we estimated a population mean and variance for the discrepancy between arms.

Method

Residents of a city-subsidized senior citizens' housing complex in Albuquerque, who voluntarily made appointments to have their blood pressures checked, comprised the study population. The subjects sat quietly for at least ten minutes before their blood pressures were determined. During this time, the following information was obtained: name, age, sex, handedness and whether or not they were taking antihypertensive medication. Their upper arm circumferences were measured 2.5 cm above the antecubital creases.

For each person the arm to be tested first was determined from a random numbers table. Without changing cuff placement, three successive readings were taken in that arm. The cuff was removed and applied to the other arm, and three more readings were done. This sequence was repeated for a total of 12 readings on each person.

An automated, electronic sphygmomanometer (IVAC Vital-Check, Model 1600) was used for all blood pressure and pulse determinations. This apparatus has automatic arm-cuff inflation and deflation, a microphone Korotkoff sound detector built into the pressure cuff and a digital display of the systolic and diastolic pressures and the pulse rate. The sphygmomanometer has been thoroughly evaluated for accuracy and reproducibility and has met the standards pro-

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posed by the American Association of Medical Instrumentation.[6]

The data were analyzed by partitioning the total variance in measured blood pressure into four components, one "between-persons" component and three "within-person" components (arm, cuff-placement and residual error). The variance decomposition was made using the the least-squares method for a three-way nested components of variance model as detailed by Graybill.[7] The computations were done using the VARCOMP procedure of the SAS statistical software package.[8] Because an order effect was noted for systolic blood pressures, adjustment for order was made before computing the variance components. This was done by specifying a fixed effect for order in the VARCOMP procedure.

The between-persons component of variance represents the variation among subjects in blood pressure. The three within-person components represent the variations in blood pressure measurements for a specific person. The within-person variation in arm represents a unique difference in the blood pressure for the right and left arms for each person. This component, along with the mean population arm difference, describes the distribution of arm effect. Assuming that this effect is normally distributed, estimates of proportions of the population with arm differences greater than a specified amount can be made.

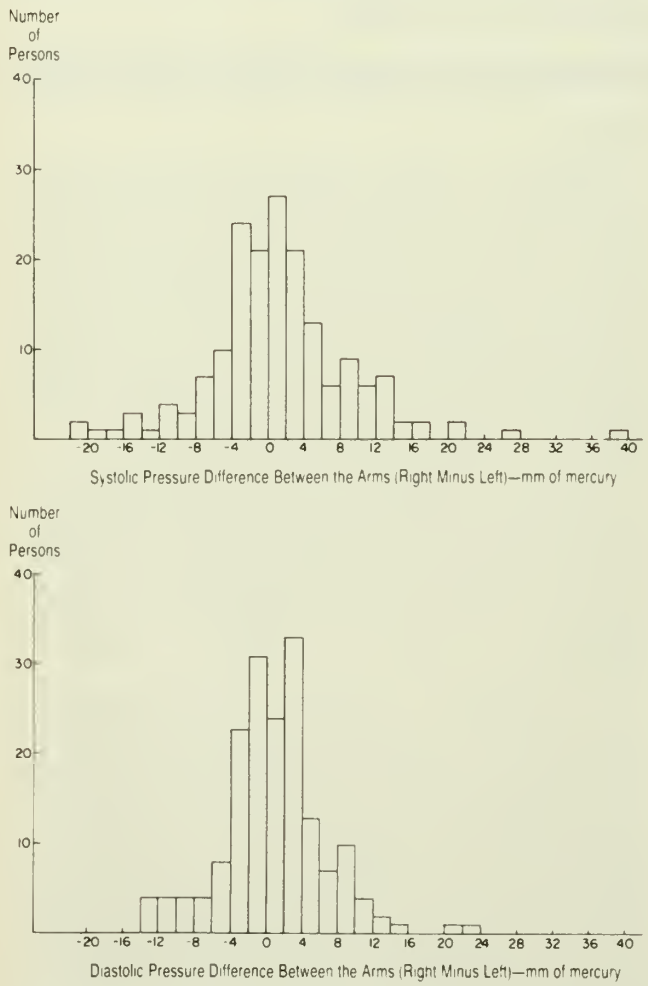
Number of Persons
40
30
20
10
-20 -16 -12 -8 -4 0 4 8 12 16 20 24 28 32 36 40
Systolic Pressure Difference Between the Arms (Right Minus Left)—mm of mercury
Number of Persons
40
30
20
10
-20 -16 -12 -8 -4 0 4 8 12 16 20 24 28 32 36 40
Diastolic Pressure Difference Between the Arms (Right Minus Left)—mm of mercury

Figure 1.—Frequency distributions of systolic and diastolic pressure differences between the arms (right and left) based on six measurements per arm.

The cuff-placement component is the measurement variation attributed to changing the position (taking it off and then reapplying it) of the pressure cuff-microphone of the Korotkoff sound-detector unit. The residual effect includes variations in physiology, technique and test apparatus.

Results

Twelve blood pressure determinations, six in each arm, were taken on 174 people, for a total of 2,088 readings. The population had a mean age of 75.8±8.9 (standard deviation [SD]) years. There were 146 women and 28 men. Most of these subjects (160) used their right hand and arm preferentially to do heavy tasks; only 14 were left-handed. The mean right arm circumference was 24.0±3.2 cm, and the mean left arm circumference was 24.0±3.3 cm. In all, 87 (50%) were taking antihypertensive medications. The mean systolic pressure was 138.5±20.0 mm of mercury and the mean diastolic pressure was 71.7±10.2 mm of mercury. The mean pulse rate was 72.9±12 beats per minute.

The 12 blood pressure readings for each person were taken three at a time, alternating the sides. Two subjects had large apparent pressure differences between the right and left sides, with either systolic or diastolic (or both) pressure differences of greater than 20 mm of mercury (right greater than left). These persons were clearly outliers from the distribution and were excluded from further analyses. The distribution of systolic and diastolic arm pressure differences is shown in Figure 1. The two persons who were excluded had the two largest diastolic differences. One of them also had the largest systolic difference.

There was a statistically significant order or sequence effect for the systolic pressures (variance ratio [F; 3,512] $=7.54$, $P<.001$). The mean of the first three readings exceeded that of the second three readings by 2.3 mm of mercury, that of the second exceeded that of the third by 0.4 mm of mercury and the third exceeded the fourth by 0.3 mm of mercury. There were no concurrent trends for diastolic pressure or pulse rate. All of the following results have been adjusted for this order effect.

The mean difference between the right and left arms (adjusted for order effect) for the population was not significantly different from zero for either systole (F [1,170]$=2.68$, $P=.104$) or diastole (F[1,170]$=3.04$, $P=.083$). The estimated mean differences (right minus left) were 0.93 mm of mercury for systole and 0.70 mm of mercury for diastole.

The estimates of the variances in blood pressure measurements are given in Table 1. The between-persons variance was large and comparable to that found in other elderly populations.[9] It was greater for systole

TABLE 1.—*Estimates of Variance Components in Measuring Blood Pressures (mm of mercury)*

Effect	*Variance Symbol*	*Variance*	*Standard Deviation*	*Coefficient of Variation*
		SYSTOLE		
Between persons . .	σ_A^2	371.0338	19.26	13.9
Within person				
Arm	σ_B^2	7.8151	2.80	2.0
Cuff-placement . .	σ_C^2	20.5577	4.53	3.3
Residual effect* .	σ_e^2	57.8052	7.60	5.5
		DIASTOLE		
Between persons . .	σ_A^2	92.7281	9.63	13.4
Within person				
Arm	σ_B^2	3.2570	1.80	2.5
Cuff-placement . .	σ_C^2	9.3913	3.06	4.3
Residual effect* .	σ_e^2	35.3658	5.95	8.3

*Variations in physiology, technique and machine. See text for a more detailed explanation.

than for diastole, though the coefficient of variation was similar in both.

The arm pressure variance within each person, σ_B^2, was significantly greater than zero for both systole and diastole ($F[170,342] = 1.39$, $P < .01$ and $F[170,342] = 1.31$, $P < .01$, respectively). This component of variance gives a specific arm effect for each person. The quantity of most interest to us was the variance, σ_d^2, of the arm difference, right minus left, in blood pressure. This variance is $\sigma_d^2 = 2\sigma_B^2$. Using estimates of σ_B^2 given in Table 1, this variance was (3.95 mm of mercury)^2 for systole and (2.55 mm of mercury)^2 for diastole.

For systole, using the mean arm difference (right minus left) of 0.93 mm of mercury and the standard deviation, σ_d, of 3.95 mm of mercury, and assuming a normal distribution, it was calculated that the proportion of persons having arm differences (either arm greater than the other) of greater than 10 mm of mercury is 1.4%. The proportions having differences greater than 7.5 and 5 mm of mercury are 6.5% and 21.8%, respectively.

For diastole, using the mean arm difference (right minus left) of 0.70 mm of mercury and σ_d of 2.77 mm of mercury, the proportion of the population having arm differences greater than 10 mm of mercury is virtually zero, and the proportions having arm differences greater than 7.5 and 5 mm of mercury are 0.5% and 8.0%, respectively. Thus, for diastole, there was little arm difference effect.

The cuff-placement component was significant both for systole ($F[342,1376] = 2.07$, $P < .01$) and for diastole ($F[342,1376] = 1.80$, $P < .01$). The variances for this cuff-placement effect were almost three times the magnitudes of the respective arm effects.

The residual component included variations in physiology, technique and machine. Instantaneous physiologic pressure variation can be related to vascular reactivity, cardiac rhythms and respiratory effects. Error can also be generated by the discontinuity in blood pressure measuring inherent in the indirect technique. The magnitude of the residual effect was much higher than that of the other within-person effects—that is, arm and cuff-placement.

There were no significant relationships between arm pressure dominance and handedness, upper arm circumferences, age, sex and whether or not taking antihypertensive medication.

Discussion

Many decades ago, investigators measured blood pressures in both arms of thousands of patients and claimed that the pressures on the right side were generally greater than those on the left.[10-12] Several criticisms might be directed at these early studies. The pressure readings were determined by standard sphygmomanometers, which can have large observer and recording biases,[13] and the orders in which the arms were tested were not randomized. Furthermore, because multiple readings were not done on each of the arms, the variance of arm pressure differences in the population could not be estimated. However, indirectly supporting their contentions of right arm pressure dominance was the lack of studies showing that the left arms were pressure dominant.

More than 20 years ago, Harrison and co-workers used newly developed intraarterial catheters and pressure inducers to measure blood pressures in both arms simultaneously in 53 subjects.[14] Unlike the previous reports, they discerned no trend of right arm pressure dominance and stated that there were no significant differences between the subjects' right and left arms. Although they recognized a beat-to-beat variation in the between-arm pressure difference, they did not randomly choose for each person those three beats that determined the arm pressure difference. There have been no recent studies of this question of arm pressure dominance.

Using an electronic sphygmomanometer, we took several blood pressure readings in both arms of elderly persons. Between- and within-person variance components were determined by a least-squares analysis of variance. There was a tendency for the right arms to have higher pressures than the corresponding left arms. Both the mean and variance for the difference between arms were small, however, indicating that only a small percentage of the population would have large pressure discrepancies.

We chose to study an elderly population because older people might have a greater chance than younger ones for having large pressure discrepancies between the arms. They tend to have elevated pressures distributed over a large range.[9] Because anatomic relations and atherosclerosis of the aorta and its large branches may be associated with pressure discrepancies between the arms,[11,12] the elderly, who have an increased prevalence of atherosclerosis, should have been more likely to have had increased arm pressure differences. That they did not suggests that the rest of the general population also does not.

To specify the arm in which pressures should be

taken seems unimportant because of the following: (1) for single readings, the difference between arms is much smaller than other unrelated effects, and (2) the probability that a person will have a clinically significant (greater than 10 mm of mercury) pressure difference between the arms is slight. One could even argue to measure pressures only in the right arm for the following additional reasons: the right arms tend to have the higher pressures, and using only one arm eliminates one, albeit small, variance component of blood pressure monitoring. Thus, for survey purposes, a policy of taking pressures only in the right arms or of not stipulating the side to be used seems reasonable.

If it is important to monitor diastolic pressures in the dominant arm when its true pressure exceeds that in the other arm by greater than 10 mm of mercury, then the following screening test can be used: (1) take three blood pressure readings in each arm, alternating the sides; (2) determine the mean for each side, and (3) that arm that had the greatest mean value should be used for subsequent monitoring. Using this test, if a person has a true diastolic pressure discrepancy of at least 10 mm of mercury between the arms, the test-designated side will be incorrect in no more than 3.3% of the cases (this is the probability that a random variable with a normal distribution of mean 10.0 and variance $\sigma^2 = 2\ [\sigma_e^2 + \sigma_c^2]/3$ is less than zero). If two pressures are taken on each side, the error will be 6.7%, and if only one reading is taken on each side, the error will be 14.5%.

Although the results of our study are general, the values of the specific screening test are apparatus-specific. Our within-person variances are larger than those reported by others who were using traditional mercury sphygmomanometers to measure pressures.[9,15] Because using our apparatus was unencumbered with the biases associated with using a traditional sphygmomanometer, it was expected that our computed within-person variances would be larger.

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Auscultatory Blood Pressure Measurement—Effect of Pressure on the Head of the Stethoscope

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Excessive pressure on the stethoscope head in auscultatory blood pressure measurement does not affect systolic blood pressure value but it does erroneously lower diastolic readings and frequently causes the sounds to persist to zero. Consequently, the lightest possible pressure should be placed on the stethoscope head.

(Londe S, Klitzner TS: Auscultatory blood pressure measurement—Effect of pressure on the head of the stethoscope [Clinical Investigation]. West J Med 1984 Aug; 141:193-195)

Current efforts relating to blood pressure have concentrated mainly on preventing, diagnosing and treating hypertension. Although it is appreciated that auscultatory measurements are not scientifically precise, observers have generally been content to accept these measurements as long as careful attention is given to controllable variables. One variable, the effect of pressure exerted by the examiner on the head of the stethoscope, has received only casual mention in the literature.[1-3] Although many clinicians are aware of this, it is our impression that it is generally disregarded. Furthermore, its effect on readings has never been documented.

We establish that pressure on the head of the stethoscope is not only a variable but is one of more than trivial importance. Our study consisted of two parts: one in which the effect of what was subjectively considered to be slight versus firm stethoscope pressure was examined and another in which the effect of pressure, quantified in millimeters of mercury and at levels unknown to the auscultator, was considered.

Subjects and Methods

Part 1

For the first part, 100 healthy adolescents, 14 to 18 years of age, were studied at the Central Juvenile Hall of the Los Angeles Probation Department. A mercury manometer, adult-size cuff and the bell end of a Littmann stethoscope were used. All measurements were made in the right arm with the subjects in the supine position. Readings were done initially in half of the boys with slight pressure on the stethoscope head, followed by a measurement with firm pressure. In the other half, the order was reversed, with the first reading obtained using firm pressure. Korotkoff phase V (cessation of sounds) was used for the diastolic signal. All measurements were made by one of us (S.L.).

Part 2

The subjects in part 2, 30 in number, were personnel and staff members of the UCLA Pediatric Department. There were 12 men and 18 women and their ages ranged from 25 to 50 years.

The observer who measured the pressures in part 1 took the readings in this part also. To eliminate any possible observer bias, measurements were made without his knowledge of how much pressure was being applied to the stethoscope head.

Two observers participated in this part of the investigation, and two mercury sphygmomanometers were used. One sphygmomanometer was connected to an adult-size cuff for the blood pressure readings, and the other was connected to a 9-cm cuff wrapped around the forearm over the stethoscope head, which was placed over the brachial artery area in the cubital fossa. The second cuff allowed varying amounts of measured pressure to be applied to the head of the stethoscope.

Measurements were made in the seated position with the arm at about heart level. Again, the bell side of the stethoscope was used. The investigator who made the

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measurements in part 1 did the listening, and a second investigator manipulated pressures in the two cuffs and recorded the readings.

Initially, a control blood pressure value was determined in the conventional manner with minimal pressure exerted on the stethoscope. The auscultator (S.L.) sat behind a screen shielding him from the subjects, the manometers and the other investigator. He was alerted each time the cuff was being inflated, and he signaled vocally when the vascular sounds appeared and disappeared.

Measurements were made with pressures of 10, 50 and 100 mm of mercury applied to the stethoscope. The sequence of these different degrees of stethoscope pressure was randomized so that the listener was at no time aware of the pressure applied to the stethoscope.

Statistical significance of values was based on the Student's *t* test.*

Results

Part 1

With light pressure on the stethoscope initially, the mean systolic pressures were 119±14.9 mm of mercury and 117±15.6 mm of mercury, respectively (± standard deviation). With initial firm pressure, the mean systolic pressures were 120±11.9 mm of mercury and 119±11.1 mm of mercury, respectively. These differences were not significant. However, there was a definite effect on the *diastolic* pressure values. Sounds persisted to zero in 42 of the 100 subjects with firm pressure but in only one with light pressure. The zero readings were excluded from the statistical analyses. Analysis of the remaining values showed, with initial light pressure, that the mean diastolic pressure was 2 mm of mercury lower with firm pressure, an insignificant difference. With initial firm pressure, however, the mean diastolic pressure was 8 mm of mercury lower with firm pressure, and this was significant ($P<.02$) (Table 1).

Part 2

The findings in part 1 were duplicated in the second part of the investigation. There was no significant effect on systolic blood pressure measurements even when as much as 100 mm of mercury pressure was applied to the stethoscope. The mean control systolic value was 115±10 mm of mercury; the mean values with 10 mm of mercury pressure on the stethoscope were 114±12 mm of mercury; with 50 mm of mercury stethoscope pressure, 115±12.2 mm of mercury, and with 100 mm of mercury stethoscope pressure, 115±12.5 mm of mercury.

All three levels of stethoscope pressure caused significant lowering of diastolic values. The readings were as follows: mean control pressure, 77±9.3 mm of mercury; 68±10.4 mm of mercury with 10 mm of mercury stethoscope pressure, and 62±18.7 mm of mercury with 50 mm of mercury stethoscope pressure. Vascular sounds persisted to zero in two subjects with 50 mm of mercury stethoscope pressure and in 23 with 100 mm of mercury stethoscope pressure, leaving too small a sample in the latter for comparison (Table 2).

TABLE 2.—*Effect on Mean Diastolic Blood Pressure Measurement of Different Measured Pressures on Stethoscope*

Number of Readings	*Diastolic Pressure mmHg±SD*	*Significance*
30 control	77± 9.3	
30 at 10 mmHg pressure	68±10.4	$P<.0001$
28 at 50 mmHg pressure*	62±18.7	$P<.0001$
30 at 100 mmHg pressure†		

SD=standard deviation

*Minus 2 zero readings.
†Only 7 of the 30 did not persist to zero, so statistical analysis was not possible.

Discussion

Only phase V was used for the diastolic signal because there is much greater certainty about the recognition of the cessation of sounds. In fact, the American Heart Association recently recommended the use of this signal for adults because "frequently the average observer has more difficulty in recognizing the muffling occurring during the fourth phase than recognizing the disappearance of sounds."[3]

"Firm" pressure (as much as 100 mm of mercury of measured pressure on the stethoscope head) obviously did not compress the brachial artery enough to prevent its opening and thus affect the systolic reading.

However, both "firm" pressure and as little as 10 mm of mercury of stethoscope pressure significantly lowered the diastolic readings. Furthermore, with "firm" pressure the sounds persisted to zero in 42% of the determinations. Similarly, with 100 mm of mercury stethoscope pressure this occurred in 77%. Even when sounds did not persist to zero, significantly lower

*M. Ray Mickey, PhD, Department of Biomathematics, UCLA, did statistical analysis of the data.

TABLE 1.—*The Effect of Firm Stethoscope Pressure on Mean Diastolic Blood Pressure Measurement*

	Number of Readings	*Light Pressure mmHg±SD*	*Number of Readings*	*Firm Pressure mmHg±SD*	*Significance*
Light pressure first	50	57±11.5	32*	55±15.8	NS
Firm pressure first	49*	60± 9.9	26*	52±16.6	$P<.02$

SD=standard deviation, NS=not significant

*Zero readings excluded.

diastolic values were observed both with firm and with measured pressure on the stethoscope.

The fact that this study was done on persons aged 14 to 50 years raises the question of whether the findings can be related to older people, many of whom have arteriosclerosis and hypertension.

It is common knowledge that in certain clinical conditions such as aortic insufficiency, hyperthyroidism and anemia, the vascular sounds may persist to zero.[4] These abnormal states produce in common a high pulse pressure. A high pulse pressure may also be related to persistence of vascular sounds in some persons who apparently have no abnormalities. Our findings suggest, however, that a more common cause is excessive pressure on the head of the stethoscope. The pressure should be so light that no skin indentations remain.

The precise mechanism responsible for the production of vascular sounds has not been firmly established, but according to Lange and Hecht,[5] they can be produced purely from disturbed flow without vibration of any physical structure. It is surprising that undue pressure on a stethoscope head has received such sparse mention in the literature because it may well constrict the brachial artery and cause turbulent flow.

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Magnified Risks From Cigarette Smoking for Coronary Prone Families in Utah

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The contribution of currently accepted risk factors to the familiality of early coronary heart disease (CHD) is poorly understood. In a telephone and mail survey, risk factor and disease morbidity and mortality data were collected from 100 proband and 185 control families encompassing about 40,000 person-years of experience. Probands were white married men who had died of CHD by age 45. There was a threefold increase in CHD incidence among first-degree relatives of probands compared with control families. In all, 67% of probands had at least one first-degree relative with early CHD, and 29% had two or more first-degree relatives with early CHD compared with 8% of the control families with two or more cases of early CHD.

The most striking new finding of this study is the apparently magnified liability of cigarette smoking in families prone to have early coronary heart disease. This effect was seen strongly at younger ages (under 50). Furthermore, in about a third of all families with a history of early CHD, smoking seemed to be the only risk factor contributing to the familial occurrence of the disease. The findings show a large excess absolute risk for CHD among smoking members of proband families and further suggest a possibly heritable susceptibility to the deleterious effects of smoking in many families prone to early coronary disease. Modification of coronary risk factors, especially cigarette smoking, would be of greatest benefit among members of high-risk families.

(Hopkins PN, Williams RR, Hunt SC: Magnified risks from cigarette smoking for coronary prone families in Utah. West J Med 1984 Aug; 141:196-202)

Death by age 45 from coronary heart disease (CHD) imposes a tragic burden on about 20,000 families in the United States each year. Effective prevention requires a better understanding of the factors leading to this extreme expression of coronary atherosclerosis. A rich understanding of risk factors for coronary heart disease in the general population has emerged from extensive studies of general populations, such as the one carried out in Framingham, Massachusetts.[1] In such studies, coronary disease before age 45 has represented such a small subgroup of cases that risk factor tabulations and analyses have not been possible.

In recent studies, coronary risk factor profiles have been reported for men and women with very early coronary disease[2-8] that indicate that a family history, cigarette smoking, hyperlipidemia and hypertension are often present. However, the fraction of cases of familial coronary disease attributable to these risk factors is unknown. Well-defined and clearly inherited receptor defects for low-density lipoprotein account for only a small percentage of coronary-prone families. Furthermore, no studies address the question of the interaction of cigarette smoking with a familial predisposition to coronary disease. In this report we present statistical evidence suggesting that cigarette smoking may have a major role in the familiality of coronary disease.

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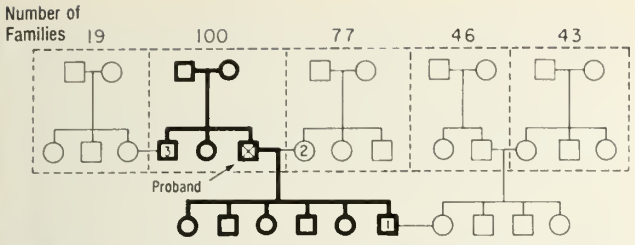


Figure 1.—A pedigree diagram shows the proband families (bold symbols) and matched control families. The three types of primary informants are indicated by numbers in the symbols and include the proband's offspring (1), spouse (2) or sibling (3).

Patients and Methods

Probands were selected from a computer file of all Utah deaths during the years 1956 through 1975, with coronary heart disease being defined as code 420 for the *International Classification of Diseases Adapted (ICDA),* seventh revision, and codes 410 to 414 for *ICDA,* eighth revision. In all there were 237 white married male Utah residents who died by 45 years of age of coronary heart disease in Salt Lake County between the years 1956 and 1975. Newspaper obituaries were obtained for 152 of these men, which represent all of the obituaries later than 1968 and a few before 1968 identified with the intent to recruit 100 proband families. Obituaries were not sought on the 85 remaining pre-1968 coronary victims as adequate response was obtained from the 152 original proband families sought. The obituaries were used together with telephone and other address directories to locate living relatives. Data were obtained through multiple mail and telephone contacts with offspring, spouse or siblings of each early coronary heart disease proband. Exclusions from the 152 original probands included 13 who had no offspring, 28 whose relatives could not be located, 4 whose located relatives refused to participate, 1 whose relative initially agreed to participate but was later lost to follow-up and 6 whose cause of death was subsequently found not to be coronary heart disease (2 rheumatic heart disease, 1 pneumonia, 1 stroke, 1 pulmonary embolism, 1 alcohol withdrawal). This left a total of 100 early coronary probands whose relatives participated in this study.

Figure 1 shows our study design. Historical information about the presence of major coronary risk factors and manifestations of coronary heart disease among proband families was obtained from offspring (46), spouses (35) and siblings (19) of the probands. In each case, information was obtained regarding the proband and his first-degree relatives (shown by the dark symbols in Figure 1), together representing the proband families who were to be characterized.

To provide comparison data, the same information was sought from a separate informant for control families (see Figure 1). The immediate family of a proband's wife and of those who married other primary informants for the proband family were sought as controls. For example, if a proband's family informant was a son, the son's wife would be a control informant. Both would be reporting information on a precisely analogous set of relatives, namely, the immediate family of their father and mother. Similarly, in the 19 cases wherein proband family informants were siblings to the proband, they would be reporting data only on their own first-degree relatives while their spouses, the control informants, reported only on their own first-degree relatives. In 35 cases, only a wife of the proband could be located as an informant, in which case she provided information on her husband's and her own immediate family.

Proband offspring with their spouses were sought preferentially as informants. A total of 46 such informant pairs participated. If offspring were not available or were unwilling to participate, wives and siblings were sought. Note that when an informant was the proband's offspring, three potential control families became available, namely, the family of the proband's wife and the family of the mother and father of the offspring's spouse. This study design provided multiple control families generally similar to the proband family with respect to age, birth cohort and other factors that would tend to be similar in spouses and close relatives.

The information sought and methods of information collection were identical for proband and control families. A detailed family questionnaire was used, with items that included name, whether living or dead, age now or at death, birth date, death date and location, weight status (slender, average, 9 to 22 kg [20 to 49 lb] overweight or 23-plus kg [50-plus lb] overweight), cigarette smoking status (never smoked, former smoker or current smoker) and the age at first diagnosis for each of the following conditions: heart attack, coronary artery bypass procedure or angina pectoris being treated medically, stroke, diabetes treated with diet or medication, high blood pressure, high serum cholesterol level and cancer.

After an initial introductory letter, telephone contact with the informant was made by a medical student who explained the procedures and began filling out the form using information supplied by the informant. This partially completed form was then mailed to the informant with instructions for obtaining and reporting the additional information required. Informants were encouraged to call relatives when necessary to obtain accurate information on the items requested. Once the forms were returned, they were reviewed by the interviewing medical student and additional telephone calls to other relatives were made as necessary to seek any missing information.

The data collection process as a whole—including obtaining obituaries, locating relatives, making several mail and telephone contacts and collecting the forms—required about eight hours of a medical student's time for each proband family with its associated controls.

There were 969 first-degree relatives of probands. Among them were 181 reported cases of coronary heart disease. Among 185 control families, there were 1,504 persons including 171 who had coronary disease. There

were about 40,000 person-years of experience for adults in age groups from 30 to 89 years.

Verifying Data

To assess the accuracy of reported mortality data, death certificate verification was carried out for a sample of questionnaires from 28 informant pairs (proband and control). Utah death certificates were found for all 116 deaths listed on these forms and compared with the information reported on the family history questionnaire. In 9% of cases, no cause of death was listed by the informant, and in an additional 6% of the cases the cause of death listed did not agree with that on the death certificate. In the remaining 85% of deaths, there was agreement between the death certificate and the reported family history. For 37 of the 116 cases, heart attack or coronary heart disease was reported by the informant as the cause of death, and in four of these cases (11%) other causes of death were listed on the death certificates. These included two cases of rheumatic heart disease, one of ruptured abdominal aortic aneurysm and one case of acute pyelonephritis in a person with chronic alcoholism. In the remaining 33 cases (89%) there was agreement between the family history report and the death certificate. Cases where cause of death was reported as unknown were counted as non-CHD deaths.

The age at death reported by an informant agreed exactly with that on the death certificate for 75% of persons, agreed within five years for an additional 18% and showed a discrepancy of more than five years in only 7% of the deaths reported on the family history forms.

As part of the continuing Utah Family Coronary Heart Disease Study, a number of families have been chosen for screening. From these families, 81 persons previously interviewed by mail and telephone queries were screened. Verification of previously reported morbidity and risk factor data was carried out by comparing actual clinic data on these 81 persons. There had been 11 cases of nonfatal myocardial infarction in this group, only one of which had not been reported. There was one case of false-positive myocardial infarction, which proved to be cardiac arrest due to hypokalemia (without infarction). The single false-negative case involved a man who had been correctly identified as having angina with onset at the same age as the myocardial infarction, hence total CHD morbidity would not have been affected by this case. There were in all ten cases of angina discovered in clinic, only two of which had not been previously reported. Both of these persons had previously had a myocardial infarction and, hence, this finding did not affect overall CHD incidence rates. There were no false-positives in this group. For stroke, there were in all four clinically confirmed histories of stroke, one of which was previously unreported, and no false-positives. Diabetes experience was similar in that four cases were confirmed in clinic—of which two were previously unreported—with no false-positives.

Assessment of weights by relatives showed close agreement with assessments on the persons themselves in clinic. In the four categories of weight (described under "Patients and Methods") there were 13, 30, 16 and 3 correctly placed in their respective categories, for an overall accuracy of 77%. For the remaining, the difference in reported and clinically verified weight category differed by only one weight level category. Reporting of cigarette smoking in relatives correlated closely with individually verified histories. There were 14 current and 11 former smokers and 50 nonsmokers, all correctly assigned; thus, smoking history was correctly reported in 93% of the cases. Extensive screening for hypertension was included as part of the clinic visit and evidence of hypertension was found in 20 of the 81 screened patients. Eighteen of these had been correctly identified by relatives and an additional five were considered in clinic to possibly have hypertension. Of these, four had previously been reported as having hypertension. There was only one person reported on the questionnaires to have hypertension who was later found to have no history of or evidence to suspect hypertension.

As might be expected, hyperlipidemia was the risk factor least reliably reported. There were, however, no false-positives in this group. Of the 81 persons screened, 25 had elevations in serum cholesterol or triglyceride level, or both. Of these, only six had been reported to have any lipid abnormality. Most of the other 19 with lipid elevations had been unaware of their serum lipid levels.

Probands were chosen for very early coronary death to maximize the contrast between their own and control families. For the purposes of tabulating family historical information, however, *early* coronary heart disease in men was defined as a reported heart attack before age 60, coronary artery bypass procedure or angina pectoris treated with medication before age 55 and the same events occurring up to five years later in women. These represent about the youngest half of all cases of coronary heart disease after excluding the proband. A positive family history was defined as at least two first-degree relatives with coronary disease, one having the onset of disease at an age at least five years younger than that in the definition of early coronary artery disease given above, and a second person with a reported coronary event at an age up to five years later than that of defined early coronary heart disease. These two groups of persons represent respectively the youngest and middle thirds of coronary events reported in study subjects after excluding the probands. This definition of positive family history correlates closely with a quantitative score that has been recently developed and described.[9] Note that positive family histories may appear within both the control group and the proband family group.

Data analyses consisted of descriptive frequency tabulations of risk factors and life-table computations of coronary disease rates. Age-specific relative risks of smoking in proband and control families were also

calculated with their 95% confidence intervals as described by Woolf[10] and Breslow and Day.[11] General linear and log-linear models[12] were fitted to the total CHD incidence rates and used to test for additive and multiplicative effects between cigarette smoking and proband versus control families.

Results

As shown in Tables 1 and 2, the rates of reported coronary events were consistently higher among the first-degree relatives of the probands when compared with the control families. This was true for both male and female relatives of the probands and generally showed a threefold increased rate of reported coronary events through most ages up to age 79. The most striking increase was reported for men with coronary events in the decade of 30 to 39 years. Probands are excluded in all of these tabulations.

The prevalence of risk factors in study subjects is shown in Table 3. The single most prominent risk factor among probands and among their relatives who have early coronary artery disease was cigarette smoking. A family history of premature coronary disease was identified among 8% of the 185 control families and 29% of the proband families after excluding the probands. If the probands are also included (the proband plus one other case of early coronary heart disease), then 67% of proband families showed a positive family history.

High blood pressure and high serum cholesterol levels were reported to be present in about a quarter of the probands and in a similar proportion of persons

TABLE 1.—*Incidence of Coronary Heart Disease (CHD) in Men in Proband and Control Families**

Age Groups Years	Total CHD Incidence			All Cases of 'Heart Attack'			Death Due to CHD		
	Proband	Control	RR†	Proband	Control	RR†	Proband	Control	RR†
30-39	3.9 (12)	0.5 (3)	7.8	3.6 (11)	0.5 (3)	7.2	1.0 (3)	0.3 (2)	3.3
40-49	9.5 (23)	3.3 (17)	2.9	8.2 (20)	2.5 (13)	3.0	2.7 (7)	1.2 (6)	2.2
50-59	29.8 (43)	11.3 (42)	2.6	28.0 (41)	9.6 (36)	2.9	17.2 (29)	2.6 (10)	6.7
60-69	29.0 (19)	10.4 (22)	2.8	25.6 (17)	9.9 (21)	2.6	17.1 (14)	7.0 (16)	2.4
70-79	44.2 (11)	27.4 (25)	1.6	38.5 (10)	22.7 (21)	1.7	49.0 (15)	20.6 (21)	2.4
80-89	31.7 (2)	33.1 (8)	1.0	44.8 (3)	22.1 (6)	2.0	41.1 (3)	17.1 (5)	2.4

*Incidence rates of new cases per 1,000 person-years. Numbers in parentheses are number of cases.
†RR (relative risk) is the CHD incidence in proband families divided by the rate in control families. Probands were excluded from the rate calculations.

TABLE 2.—*Incidence of Coronary Heart Disease (CHD) in Women in Proband and Control Families**

Age Groups Years	Total CHD Incidence			All Cases of 'Heart Attack'			Death Due to CHD		
	Proband	Control	RR†	Proband	Control	RR†	Proband	Control	RR†
30-39	1.5 (5)	0.3 (2)	5.0	1.2 (4)	0.3 (2)	4.0	0.3 (1)	0.0 (0)	...
40-49	4.6 (12)	1.3 (7)	3.5	3.8 (10)	1.1 (6)	3.5	2.3 (6)	0.2 (1)	11.5
50-59	9.6 (18)	2.9 (11)	3.3	7.9 (15)	1.6 (6)	5.0	3.5 (7)	0.5 (2)	6.8
60-69	28.0 (26)	6.5 (14)	4.3	25.6 (25)	6.4 (14)	4.0	11.6 (13)	2.7 (6)	4.3
70-79	19.7 (8)	10.3 (11)	1.9	18.7 (8)	7.3 (8)	2.6	18.6 (9)	2.6 (3)	7.1
80-89	18.2 (2)	31.6 (9)	0.6	8.8 (1)	33.4 (10)	0.3	33.1 (4)	21.4 (7)	1.5

*Incidence rates of new cases per 1,000 person-years. Numbers in parentheses are number of cases.
†RR (relative risk) is the CHD incidence in proband families divided by the rate in control families. Probands were excluded from the rate calculations.

TABLE 3.—*Factors in Persons With and Without Coronary Heart Disease (CHD) in Proband and Control Families*

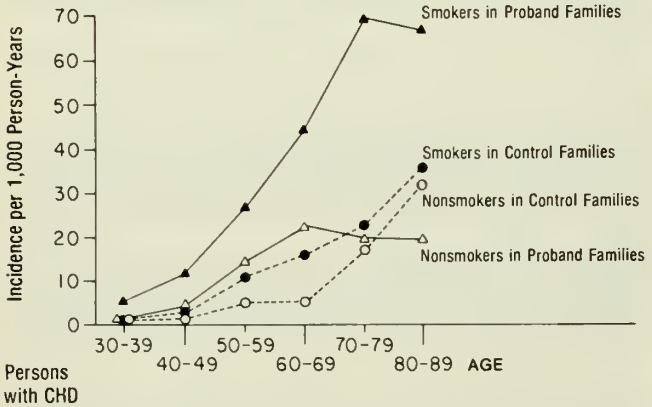
Study Subjects	Number	Mean Age Years	Prevalence Rates (%)					
			Smoking	Hypertension	Hypercholesterolemia	Obesity	Diabetes	Stroke
Probands With Early CHD	100	41	84	19	24	1	2	3
*Other Men With Early CHD**								
Proband families	78	56	72	31	20	4	3	5
Control families	62	58	39	37	26	11	5	8
Early CHD in Women								
Proband families	51	60	37	33	14	12	16	14
Control families	28	60	15	42	7	14	18	18
Men Without CHD†								
Proband families	361	41	47	14	4	2	3	3
Control families	601	51	47	12	1	4	4	4
Women Without CHD†								
Proband families	427	43	25	16	4	8	5	6
Control families	731	51	22	17	1	7	5	5

*Refers to men other than the probands in whom early CHD developed. Early CHD is defined as, in men, a heart attack before age 60 or treated angina pectoris (including coronary artery bypass grafting procedure for angina) by age 55. For women, the same events occurring at an age 5 years older are considered early CHD.
†Persons free of CHD at any age.

with early coronary disease in both proband and control families. Obesity and diabetes were not frequently present in the probands or other men with early coronary disease but were reported more often among women with early coronary disease in both proband and control families. For persons without coronary disease, the prevalence of risk factors was very similar in proband families and control families.

The most striking results of this study relate to the interaction between smoking and membership in a proband family. Figure 2 shows the annual incidence rates of coronary heart disease in age-specific groups for smokers and nonsmokers in proband families (probands excluded) and in control families. As expected, the incidence of coronary disease is consistently higher among smokers than among nonsmokers, in both proband families and control families. Analysis of variance using a linear model of the incidence rates showed that the effect of smoking was more than additive in proband families compared with controls ($P<.0001$). This result implies that smoking at least multiplied the risk associated with membership in a proband family. Thus, if being a member of a proband family carries a relative risk of 3 and smoking a relative risk of 2, then a smoking proband would have a relative risk of at least 6.

The relative risk associated with smoking in proband families may be greater than that in control families (Figure 2). This possibility was tested by analysis of variance using a log-linear model of the incidence rates, which revealed an exponential effect between cigarette smoking and membership in a proband family that was of borderline significance (P .053). In addition, 95% confidence intervals for the age-specific relative risks for smoking in proband and control families were calculated (Table 4) and showed that the relative risk for smoking among the proband families is outside the



Persons with CHD	30-39	40-49	50-59	60-69	70-79	80-89
▲	13	23	31	20	9	1
△	4	12	30	25	10	3
●	0	10	28	20	10	3
○	5	14	25	16	26	14

Figure 2.—The age-specific annual incidence of coronary heart disease (CHD) is shown for cigarette smokers and nonsmokers in the families of probands with early CHD and in control families. The number of incident CHD cases reported in each age and family group is listed in the table.

95% confidence interval of relative risk for smoking in control families in three of the six age categories and in the summary of relative risk. Of note is the fact that the largest differences in relative risk are seen in the two younger age categories. Thus, proband family members appear to show greater susceptibility to risks of smoking, especially those persons younger than 50 years.

In an attempt to explore which risk factors might possibly explain the familial aggregation of CHD, families with a history of CHD by our definition—that is, all families from both proband and control groups with a positive family history—were examined. Risk-factor concordance in these selected families was then tabulated. Concordance within a given family for risk factors other than smoking was considered to be present if two or more of the persons affected with early coronary disease were also reported to have the risk factor. For smoking, more than 50% of the affected persons had to be smokers for there to be concordance in a family. Probands were included in the family for concordance tabulations (Table 5). Note that both control and proband families show a history of CHD. This analysis of concordance in these families is not intended to yield data precise enough for statistical analysis. Rather, it is a qualitative or semiquantitative reflection of which risk factors might possibly contribute to familial aggregation of disease.

Cigarette smoking was clearly the most common concordant risk factor, being reported as the only risk factor shared by early CHD victims in 20% of the

TABLE 4.—*Relative Risks of Smoking in Proband and Control Families**

Age Categories		*Relative Risk*	*(95% Confidence Interval)*
30-39	Probands	4.8†	(1.6 - 15.0)
	Controls	0.2‡	(0.007 - 3.4)
40-49	Probands	3.0†	(1.4 - 6.1)
	Controls	1.3	(0.6 - 2.9)
50-59	Probands	2.0	(1.1 - 3.4)
	Controls	2.1	(1.2 - 3.7)
60-69	Probands	2.0	(1.0 - 3.9)
	Controls	2.9	(1.5 - 5.8)
70-79	Probands	3.6†	(1.2 - 10.4)
	Controls	1.3	(0.6 - 2.9)
80-89	Probands	3.5	(0.3 - 45.3)
	Controls	1.2	(1.2 - 4.5)
Summary All Ages	Probands	2.5†	(1.8 - 3.5)
	Controls	1.7	(1.3 - 2.4)

*Confidence intervals and all ages summary statistics calculated according to the logit method of Woolf[11] as outlined by Breslow and Day.[12]
†Relative risk above 95% confidence interval of control.
‡Estimate by addition of ½ to all cells according to Breslow and Day.[12]

TABLE 5.—*Risk Factors Possibly Accounting for Familial Coronary Heart Disease (CHD) Among Families With a History of CHD*

Risk Factor*	Families With Risk Factor Concordance: Proband Families With Positive Family History N=29 Percent	Families With Risk Factor Concordance: Control Families With Positive Family History N=15 Percent
Cigarette smoking all†	66	47
Cigarette smoking only‡	34	20
Hypertension	38	33
Hypercholesterolemia	28	20
Diabetes mellitus	0	7
Obesity	0	0
None	14	27

*Risk factor categories are not mutually exclusive. About 25% of families had two or more common risk factors present in the same persons with early CHD.
†Concordant for cigarette smoking plus other risk factors.
‡Concordant only for cigarette smoking.

control families and 34% of the proband families with a positive family history. Hypertension and hypercholesterolemia were also possible underlying risk factors in a large proportion of families, and about 25% of families showed concordance for two or more risk factors. In a substantial number of families, relatives with coronary disease did not seem to share any risk factor that would account for their family's increased risk.

Discussion

The methodology in the present study has several strengths as well as limitations. Using this family history data collection approach, information has been assembled with an approximate number of person-years and coronary events equivalent to ten years of data collection in the Framingham study, with far less expense and in a much shorter period of time. By using the case-control approach, information was collected in a subset of persons and families with very early coronary heart disease for whom prospective studies such as the Framingham study had too small a representation for adequate analysis.

The main limitation of this study is that it is based on historical data reported by persons with no medical training. A comparison of death certificates with information reported on the family histories indicated age at death was accurate within five years in 93% of the tested sample. Verification of nonfatal coronary heart disease morbidity data for a subset of 81 clinically screened persons showed questionnaire-reporting sensitivity of about 90%, with only one false-positive in 19 reported cases of angina and myocardial infarction. Smoking history was accurately reported in mail questionnaires or telephone interviews, with 93% of the 81 screened persons being correctly assigned to current or former smoker or nonsmoker categories. Thus, the accuracy of the key variables in this report is considered to be about 90%.

A comparison of the age-specific coronary mortality rates from the Utah Vital Statistics with the rates derived from these family history data suggests that coronary heart disease may be underreported. The coronary death rates from control families were consistently 15% lower than the Utah Vital Statistics rates in age- and sex-specific categories during the period 1956 through 1975. As expected, the rates in the high-risk proband families were considerably higher than the Utah Vital Statistics data, consistently showing a twofold to fourfold increase in age-specific categories.

Complete information regarding CHD incidence is not available for the general Utah population. When the coronary incidence rates from these family history data are compared with those of the Framingham study, the Utah control families showed age-specific CHD incidence that was consistently 20% below the Framingham rates. This could be due in part to the significantly lower rate of smoking in Utah and the associated lower CHD mortality rates in Utah compared with those of the general US population.[13]

There is likely some underascertainment of risk factors in these historical data. Some of the family members may have had risk factors that were not known to the informant and other family members may have had risk factors such as hypertension or hypercholesterolemia that were undetected. In fact, of the 25 cases of hyperlipidemia found among a subset of 81 persons screened, fully three fourths of the persons had not been aware that they had any lipid abnormalities. Fortunately, the most important findings in this study related to those on cigarette smoking, which informants usually knew with confidence regarding their close family members.

The prevalence in this study of risk factors in probands with coronary death before age 45 is in excellent agreement with a recently reported study of 120 men who had myocardial infarction before age 36 and angiographically substantiated coronary artery disease. In that study, 89% were smokers, there was a positive family history in 48%, hypertension in 21% and lipid abnormalities in 20%.[2] Other studies report similar results.[3,4] Probands in the present study had nearly identical findings, as shown in Table 3. None of these reported studies nor our current report indicates that diabetes or obesity plays a significant role in very early coronary heart disease in men, whereas in women who were early CHD victims, these risk factors figure prominently along with those seen in men.[5-8]

The most striking new finding of this study is the apparent magnified relative risk of smoking among first-degree relatives of early CHD probands. This effect was most strongly seen in members of proband families younger than 50 years. Furthermore, in about 30% of the high-risk families identified in this study, smoking appeared to be the only risk factor shared by individuals with early coronary heart disease. It is possible that a familial susceptibility to the harmful effect of smoking is operating in these families. Possible mechanisms for such an effect could involve the interaction of smoking with platelet or clotting factors or enhanced smoking-induced endothelial damage. Effects

of smoking in these processes have already been suggested by past studies.[14] Oral contraceptives have been shown to potentiate the risk of myocardial infarction from cigarette smoking in young women.[6-8] In like manner, inherited factors may potentiate the effects of cigarette smoking in some coronary-prone families. Another possible explanation for these results involves the precipitating effect of cigarette smoking that potentiates platelet aggregation and clotting factor activity. Thus, in persons with far-advanced stenosis of coronary arteries, cigarette smoking could precipitate an acute thrombotic event.[14] When members of proband families have far-advanced disease at early ages, the effect of cigarette smoking is greatly magnified. The observation that many families reported no risk factor other than cigarette smoking also indicates that cigarette smoking may promote atherosclerosis at earlier stages of the disease.

The interaction between cigarette smoking and membership in proband family as reported here is a new finding. Previous studies such as those in Framingham or Tecumseh have not assessed family history by combining all first-degree relatives. Furthermore, family history has not been included in the multiple regression analyses of risk factors in those studies. A recent analysis of disease experience in sibling pairs from the Framingham study has shown a significant independent effect of a positive family history (defined as coronary disease at *any* age in one sibling) for predicting subsequent disease in a younger sibling.[15] In that study, however, smoking did not contribute significantly to disease prediction in the multiple logistic equation, possibly due to a nonspecific definition of a positive family history and only a few cases of early coronary disease that had the strongest interaction in this study. In a study by Rissanen and Nikkila[16] hypertension and hypercholesterolemia appeared to cluster in families with a history of coronary heart disease. However, these investigators were unable to estimate the contribution of hypertension or hypercholesterolemia to the excess risk of coronary disease among their families. Furthermore, they did not report on smoking experience.

The results of our study have significant implications for preventing early coronary heart disease. The occurrence of coronary heart disease in these high-risk families appears to depend on both an inherited predisposition and interacting environmental factors. Because smoking at least multiplies baseline risks, a person who is already at high risk for coronary heart disease due to genetic factors who subsequently chooses to smoke is at a much greater absolute risk for development of heart disease than a smoking counterpart from a family with no excess coronary risk. The possibly synergistic interaction of cigarette smoking and family history suggested by increased relative risks for smoking in younger age groups reported here further emphasizes the high absolute risk associated with smoking in familially predisposed persons. Thus, members of high-risk families should benefit even more from efforts aimed at smoking cessation than would persons in the general population. Some physicians seem to have a misconception that if coronary disease occurs on the basis of a strong familial predisposition, little can be done to help members of these high-risk families: "Since you can't change their genes, you can't reduce their risk." This study indicates just the opposite. Modification of coronary risk factors may benefit members of high-risk families the most.

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Febrile Gastroenteritis Due to *Salmonella thompson*

Report of an Outbreak

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Salmonella thompson, *a common pathogen of poultry, has received scant attention as a cause of human gastroenteritis. At least 45 persons were infected with* S thompson *in Sacramento, California, after eating at a chicken restaurant and 38 became symptomatic. Ten required admission to hospital, and all were treated with antibiotics and improved. In 19 cases cultures of stool specimens for* S thompson *over a 60-day period showed slower but statistically insignificant differences in salmonellal elimination in 7 patients who received antibiotics when compared with 12 who were untreated. We report this outbreak to increase awareness of the virulence and prevalence of gastroenteritis due to* S thompson.

(Linares AP, Cohen SH, Goldstein E, et al: Febrile gastroenteritis due to *Salmonella thompson*—Report of an outbreak. West J Med 1984 Aug; 141:203-205)

Except for occasional case reports and notations in epidemiologic communications, *Salmonella thompson* has received scant attention as a cause of gastroenteritis.[1-5] Recently, *S thompson* caused an outbreak of gastroenteritis in Sacramento, California, in which at least 45 persons were infected and 10 required admission to hospital. In researching this species, we found that although *S thompson* is infrequently discussed in the literature, it is often listed as a cause of gastrointestinal infection and bacteremia.[6,7] We are therefore reporting this outbreak to increase awareness of the virulent gastroenteritis caused by *S thompson.*

Patients and Methods

A total of 45 persons who ate at a chicken restaurant within a four-day period were found on the basis of positive stool cultures to be infected with *S thompson.* They were interviewed within a week to determine the time of exposure and the onset, duration and type of symptoms. In all, 38 had gastrointestinal symptoms; 19 had sought medical attention and their medical records were reviewed. Ten who were admitted to hospital were studied as a separate subset to evaluate the effect of the infection on blood counts, chemistry determinations and blood culture results. Seven of the ten had stool specimens examined for fecal leukocytes and blood specimens were drawn from six to test the development of antibody to *S thompson.*

Stool specimens from 19 patients were cultured for *S thompson* over a 60-day period to determine differences in duration of excretion related to antibiotic treatment. This group comprised seven patients who were symptomatic and received antibiotics, eight patients who were symptomatic but did not receive antimicrobial therapy and four who were asymptomatic.

The source of the outbreak was investigated by the Sacramento County Health Department. This investigation included cultures of leftover foods purchased by infected persons and foods found at the restaurant.

Stool specimens were plated on MacConkey, Hektoen and VPTC agar. Lactose nonfermenting Gram-negative rods that fulfilled the biochemical and cultural criteria for *Salmonella* and that agglutinated with *Salmonella* polyvalent antiserum were further identified as *Salmonella thompson* by the California State Laboratories, Berkeley, using specific antiserum for group

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TABLE 1.—*Symptoms in 38 Patients With Gastroenteritis Due to* Salmonella thompson

Symptoms	*Patients Affected*	
	Number	*(Percent)*
Fever	21	(55)
Chills	13	(34)
Nausea	11	(29)
Vomiting	16	(42)
Abdominal cramps	20	(53)
Diarrhea	27	(71)
Headache	5	(13)

TABLE 2.—*Influence of Antibiotic Treatment on Excretion of* Salmonella thompson *in Feces*

Treatment Group	*Number*	*Number Positive*	
		at 30 days (Percent)	*at 60 days (Percent)*
Untreated	12	3 (25)	1 (8)
Antibiotics*	7	4 (57)	1 (14)

*Six patients were treated with parenteral chloramphenicol, 50 mg/kg/day for 3 days, followed by ampicillin by mouth, 50 mg/kg/day for 7 days. One patient was treated with 1 double-strength tablet of trimethoprim-sulfamethoxazole twice a day for 14 days.

C_1 antigens. The infecting strains were also tested for plasmids by Dr Mark Finch of the Enteric Disease Branch of the Centers for Disease Control, Atlanta. Minimal inhibitory concentrations of ampicillin, cefazolin sodium, chloramphenicol, tetracycline, carbenicillin, gentamicin, tobramycin sulfate, amikacin sulfate and trimethoprim-sulfamethoxazole were determined for the *S thompson* isolate by microtiter dilution techniques. Acute and convalescent antibody liters to *S thompson* were measured with a whole-cell agglutination method using a preparation containing group C antigens (Sylvania).

Results

Chicken scraps, gravy and beans collected at the homes of infected persons grew *S thompson. S thompson* was not cultured from raw chicken or other products found at the restaurant five days following the outbreak. Table 1 shows that 38 patients were clinically symptomatic with fever (21), chills (13), nausea (11), vomiting (16), abdominal cramps (20), diarrhea (27) and headache (5). The incubation period varied from 2.5 to 24 hours with a mean of 8 hours. The patients who were not admitted to hospital recovered within a few days. The ten patients requiring hospital care were more seriously ill. Their average incubation period was six hours. Their temperatures varied from 38.7°C to 40.3°C (101.6°F to 104.6°F) and they had severe gastrointestinal symptoms that persisted for 4 to 14 days. The laboratory data from these ten patients showed normal leukocyte counts of 5,300 to 11,700 per μl and large increases in band forms in the differential count. Elevations in serum enzyme activity were noted for alkaline phosphatase (two patients), aspartate aminotransferase (glutamic-oxaloacetic transaminase; two patients) and lactic dehydrogenase (one patient). Nine patients had blood cultures and one set grew *S thompson*. Four of seven stool specimens contained numerous polymorphonuclear leukocytes. In four of six patients who were tested for agglutinating antibody to *S thompson*, fourfold or greater increases in titer developed. In contrast, in none of six symptomatic patients who were not admitted to hospital did significant increases in antibody titer develop. All patients treated in hospital recovered without complications.

Table 2 contains the data for the 19 patients who had multiple stool cultures over a 60-day period. Although the differences are not statistically significant, a higher percentage of patients who received antibiotics excreted *S thompson* in their stools at 30 and 60 days after infection.

Plasmids were not found in the *S thompson* cultured from patients or from foods collected in homes and at the restaurant. The antibiograms for the *S thompson* that was recovered from the three sites were identical.

Discussion

Salmonella thompson is one of the commonest *Salmonella* serotypes infecting poultry and outbreaks are often traced to this source.[1,2,4,7,8] Investigation of the present outbreak also incriminates chicken as the probable source of infection. Chicken and gravy scraps and beans purchased from the restaurant were identified as infected foods. Because *S thompson* was not cultured from raw chicken or other products obtained at the restaurant and because employees had *S thompson* cultured from their stool specimens, it is possible that a restaurant employee who was a carrier of *S thompson* infected these products. However, because the outbreak was sharply limited and none of the employees were new, we believe that the employees, like the patrons, became contaminated and that the chicken itself was the source. Contamination of gravy and beans then permitted these foods to also serve as the vehicles for infection.

The virulence of the *S thompson* serotype is attested to by the number of patients in whom severe gastroenteritis developed. Similar virulence has been noted in previous outbreaks.[1,2] In Peru, 545 of 598 university students required admission to hospital after eating eggs contaminated with *S thompson* in the school dining room.[1] In another outbreak in Louisiana, gastroenteritis developed in 200 of 201 persons and 18 required admission to hospital. Two patients died in this outbreak.[2]

The laboratory data for the ten in-hospital patients showed that infection with *S thompson* resulted in few abnormalities. The hemograms were normal except for increases in the number of immature polymorphonuclear leukocytes. Results of hepatic and renal function tests were also normal, except for a few mild elevations in serum aspartate aminotransferase, alkaline phosphatase and lactic dehydrogenase values. *Salmonella* bacteremia occurred in only one patient, which is consistent with the reported infrequency of this event.[6] As in other studies, fecal leukocytes, which were present

in four of seven patients, were a helpful but diagnostically nonspecific finding.[9] The increases in agglutinating antibody titer in four of six patients treated in hospital, as compared with none of six outpatients, probably reflects the severity of infection. Agglutinins develop unpredictably in cases of intestinal salmonellosis and absences in antibody response are common.[10,11]

Although the differences are not statistically significant, the finding that a higher percentage of patients who received antibiotics excreted *S thompson* in their stools at 30 and 60 days after infection accords with published results showing that antimicrobial therapy prolongs the carrier state.[12,13] It is worth emphasizing that the number of carriers represents a small percentage of the infected population at two months after infection with only 2 of 19 patients having positive stool cultures. Because antibiotics prolong the carrier state and may not reduce morbidity in uncomplicated enterocolitis, many authorities discourage their use in this clinical situation.[10,12,14] These authorities recommend that antimicrobial treatment be restricted to seriously ill patients with enteric fevers, focal infections or underlying impairments in immune mechanisms.[10,14] On the basis of our observations in patients admitted to hospital with *S thompson* infection, we believe this therapeutic recommendation should be broadened to include patients who are seriously ill with gastroenteritis and in whom blood culture results are pending. Future studies may show that antimicrobial therapy is fruitless, but without this evidence it seems prudent to attempt to suppress infection in these toxic patients even if it increases the likelihood of a carrier state developing.

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Medical Progress

Reye's Syndrome

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Reye's syndrome (encephalopathy with fatty infiltration of the viscera) is an acute illness of childhood that produces hepatic dysfunction and metabolic encephalopathy. The disease is fatal in as many as 40% of cases. The cause is unknown. Several environmental agents, particularly salicylates and aflatoxin, have been implicated as possible toxins in this disorder. Treatment is directed at controlling intracranial pressure, reversing metabolic abnormalities and providing intensive supportive care. Normal neurologic function returns in most survivors.

(Trauner DA: Reye's syndrome [Medical Progress]. West J Med 1984 Aug; 141:206-209)

A great deal of publicity has surrounded recent information relating to Reye's syndrome. This disorder, which was first described in 1963 as a specific entity of encephalopathy with fatty infiltration of the viscera,[1] occurs most commonly in infants and children younger than age 17 years and only rarely in adults. The incidence is estimated at 0.31 cases per 100,000 children younger than 17 years,[2] though in at least one report there was an elevenfold higher incidence (3.5 cases per 100,000 children)[3] when milder, biopsy-proved cases are studied. Cases occur both sporadically and in "epidemics," the latter primarily following influenza outbreaks. Although cases occur throughout the year, there is some seasonal predilection, with late winter and early spring being "peak" times.[4]

Reye's syndrome has some interesting epidemiologic features for which there is no clear explanation. The disease tends to occur in white, middle-class children who live in suburban and rural areas.[4] The opposite appears to be true for infants younger than 1 year; these cases are more likely to occur in poor, inner-city dwellers and among members of ethnic minorities.[5]

Clinicopathologic Features

Reye's syndrome is a biphasic illness. The prodrome is a viral infection, with upper respiratory or gastrointestinal tract symptoms. Viruses most often associated with the disorder are influenza-B and varicella. Typically a child is recovering from this illness when the acute onset of recurrent vomiting develops, which progresses to encephalopathic symptoms (lethargy, agitation, delirium or coma) within 24 to 48 hours after vomiting begins. Seizures may occur at any time during the encephalopathic phase[6] but are more frequently seen in infants and younger children.[5] Respiratory abnormalities are common, with hyperventilation being most prominent. Apneic episodes may occur, particularly in infants.[5] The liver is often enlarged, but patients are anicteric. The disease may progress to deep coma with evidence of brain-stem dysfunction and occasionally is fatal (10% to 40% of cases).

Increased intracranial pressure is a common and severe complication.[7,8] Occasionally, acute pancreatitis may also complicate the clinical findings.

Results of laboratory investigations (Table 1) show evidence of liver dysfunction with elevated serum aminotransferases, hyperammonemia and a prolonged prothrombin time. The serum bilirubin value is normal. Hypoglycemia occurs in about 40% of patients and is encountered more frequently in children younger than 4 years.[6] Respiratory alkalosis is usually found, often with a concomitant metabolic acidosis. Creatine phosphokinase concentrations are elevated in serum.

Other laboratory abnormalities known to occur in Reye's syndrome include free fatty acidemia,[9] elevations in serum amino acid levels,[10] hyperuricemia and lactic acidemia.[6] Examination of the cerebrospinal fluid shows no abnormalities except for increased pressure and occasional hypoglycorrhachia in conjunction with hypoglycemia.

The most obvious pathologic abnormality by light microscopy is diffuse panlobular microvesicular fatty accumulation in the liver (Figure 1). Fatty infiltration may also be found in specimens from kidney, heart and skeletal muscle. Histochemical stains have revealed depletion of succinic acid dehydrogenase activity in the

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TABLE 1.—*Hematologic and Metabolic Abnormalities in Cases of Reye's Syndrome*

↑ Leukocyte count
↑ Ammonia
↑ Serum aminotransferases
↑ Prothrombin time
↑ Creatine phosphokinase
↓ Serum and cerebrospinal fluid glucose
Respiratory alkalosis
Metabolic acidosis
↑ Serum short- and medium-chain fatty acids
↑ Amino acids (lysine, glutamine, alanine, α-amino-*N*-butyrate)
↑ Lactic acid
↑ Uric acid
↑ Blood urea nitrogen
↑ Amylase
↑ Cerebrospinal fluid glutamine
↓ Serum C1 and C1S complement activity

↑ = increased, ↓ = decreased

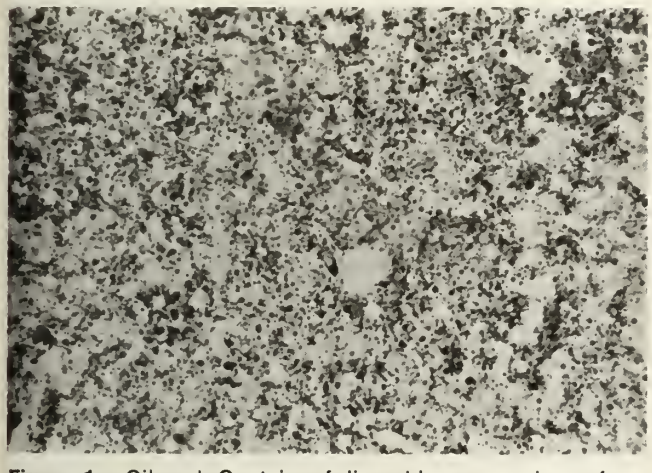

Figure 1.—Oil red O stain of liver biopsy specimen from patient with Reye's syndrome showing diffuse, microvesicular fatty infiltration. (Reduced from magnification × 600.)

liver.[11] Ultrastructural changes in liver mitochondria include swelling and pleomorphism, irregularity of the mitochondrial membrane and diminution of matrix granules.[12]

The principal neuropathologic change is the presence of diffuse cerebral edema. Changes due to anoxia may be observed. Brain mitochondrial abnormalities similar to those in the liver have been reported. The pancreas may have areas of focal necrosis, hemorrhage and inflammation.

Role of Salicylates and Other Toxins

The cause of Reye's syndrome is unknown. It is not the direct result of a viral infection such as encephalitis or hepatitis. Several hypotheses have arisen, including a viral toxin interaction, genetic predisposition and release of endogenous toxins. The possible role of aspirin in the etiology of Reye's syndrome has received much publicity in the past few years.

The possible involvement of salicylates was suggested as early as 1962, even before Reye's syndrome was recognized as a clinical entity. Mortimer and Lepow[13] reported four cases of infants with varicella infections who had received aspirin. In two of these clinical and pathologic features developed that were compatible with Reye's syndrome. In 1975 Linneman and co-workers[14] reviewed 56 patients with pathologically confirmed Reye's syndrome, 53 of whom had a history of salicylate ingestion. Two years later, Corey and associates[15] reported that 78% of 175 patients with Reye's syndrome had received aspirin and suggested a possible correlation. In recent studies from Arizona,[16] Ohio and Michigan,[17,18] case-control methods were used to study the possible relationship between salicylates and Reye's syndrome. Each study compared known cases of Reye's syndrome with control children of similar ages in whom viral illnesses developed similar to the prodrome of the children with Reye's syndrome. None of the control children were admitted to hospital for their illness. The studies used questionnaires answered by the parents after the illnesses were identified. Parents were interviewed anywhere from two days to six weeks after the onset of the illness in both patients and controls. In all of the studies, patients with Reye's syndrome had taken salicylate-containing medications during the prodromal illness much more frequently than control children, even when the two groups were matched for fever, and Reye's syndrome patients took more salicylates than non-Reye's syndrome controls who had taken salicylates. These findings suggested a possible causal relationship between salicylate ingestion during the prodromal illness and the subsequent development of Reye's syndrome.

These reports have led to a great deal of discussion about the safety of administering aspirin in viral illnesses. There are several difficulties with this type of study. There may be "recall bias," in which parents of more severely ill children tend to remember details of the illness more accurately than parents of less severely ill children. Also, parents whose children are more severely ill may try more medications to treat that illness and this may explain the more frequent use of salicylates in the Reye's syndrome group. There may be mismatching of the severity of the prodromal illness in Reye's syndrome versus control children. For example, many more of the children in whom Reye's syndrome developed had fever during their prodrome than did the control children.

After reviewing the data, including arguments regarding the limitations of the case-control method, the Committee on Infectious Disease of the American Academy of Pediatrics concluded that, despite potential pitfalls in the study, there was a "high probability that the administration of aspirin contributes to the causation of Reye's syndrome" and that aspirin "should not be prescribed under usual circumstances for children with varicella or those suspected of having influenza."[19]

In addition to the case-control studies, there are other data that suggest at least a possible relationship between salicylates and Reye's syndrome. Clinically, there are many similarities between Reye's syndrome and salicylate toxicity. These include encephalopathy, hyperven-

tilation, abnormalities in liver function, metabolic acidosis, respiratory alkalosis and occasionally fatty changes in the liver. In experimental animals, salicylates are known to uncouple oxidative phosphorylation[20] and may, thus, impair energy metabolism. It is conceivable, therefore, that salicylates may potentiate the adverse effects of certain viruses on mitochondrial function and in this way lead to the development of Reye's syndrome.

Salicylates are not the only answer, however. Many children with Reye's syndrome have not taken any salicylate-containing compound. Also, this would not explain why millions of children take aspirin for viral illnesses and Reye's syndrome never develops.

A Reye's-like illness in Thailand is known to be caused by aflatoxin, a metabolite of the fungus *Aspergillus flavus*.[21] Aflatoxin is found in corn and peanut products. In several reports in the United States, aflatoxin was found in blood or tissue specimens of patients with Reye's syndrome.[22,23] Other investigators have been unable to find any association of aflatoxin, however. Jamaican vomiting sickness has symptoms similar to those of Reye's syndrome and is caused by ingesting hypoglycin A, a compound found in unripe akee fruit.[24] In experimental animals, a Reye's-like syndrome can be produced by administering 4-pentenoic acid, a derivative of hypoglycin A.[25] Another experimental model has been devised using a combination of virus infection and insecticide applied to the animal.[26] Thus, there appears to be more than one environmental toxin that can produce symptoms of Reye's syndrome.

There are other etiologic considerations as well. Thaler[27] has suggested a possible genetic predisposition or inborn error of metabolism as the underlying factor in the development of Reye's syndrome. Some of the urea-cycle disorders, as well as systemic carnitine deficiency, can resemble Reye's syndrome. Finally, endogenous toxins may be liberated during a viral illness that could result in encephalopathy and other changes of Reye's syndrome. Short- and medium-chain fatty acids are elevated in the serum of patients with Reye's syndrome.[9] These compounds, when injected into experimental animals, reproduce the major clinical, pathologic and biochemical features of Reye's syndrome.[28,29] It has recently been shown that experimental influenza B infection in mice results in a block in mitochondrial β-oxidation of fatty acids with subsequent elevations in serum free fatty acid concentrations.[30] A mechanism such as this may be responsible for the development of the symptoms of Reye's syndrome. Ammonia has intermittently been implicated as the endogenous toxin possibly responsible for hepatic encephalopathy and Reye's syndrome. Several investigators have found an association between serum ammonia concentrations and the severity of the disease.[31,32] In experimental animals injected with high concentrations of ammonia-containing salts coma developed, though the serum concentrations of ammonia that are required to produce coma in experimental animals far exceed the usual degree of hyperammonemia in children with Reye's syndrome.[33]

In summary, more than one etiologic factor are likely responsible for the development of the symptom complex known as Reye's syndrome. Until there is more specific knowledge about the pathogenesis of this disorder, however, it would seem prudent to try other means of reducing fever and discomfort in children with viral illnesses and, in particular, flulike illnesses and varicella, before resorting to salicylate treatment.

Treatment

Most treatment protocols cover three general areas: intensive supportive care, correction of metabolic abnormalities and treatment of increased intracranial pressure. Because the etiology of the disorder has not been determined, no specific therapeutic approach has been identified.

Any child suspected of having Reye's syndrome, even in the early stages, should be admitted to a pediatric intensive care unit for careful observation. Evaluation of a child with Reye's syndrome involves assigning an appropriate stage to the disease. Children with stage 1 disease are lethargic but able to follow verbal commands, have purposeful responses to pain and evidence of hepatic dysfunction. Stage 5 is the most severe, and in this case the child is in coma with flaccid muscle tone, no response to pain, no oculocephalic reflexes and pupils may be unresponsive to light. For stages 1 and 2, patients are generally treated with intravenous administration of hypertonic glucose solutions, are monitored frequently for respiratory or blood pressure changes and observed closely.[3] For stages 3 through 5, a variety of treatment protocols exist. In our center, the following is used.[34] Nasotracheal tubes are electively inserted and arterial and central venous pressure lines, as well as nasogastric tubes and Foley catheters. Mechanical ventilation is used and patients are paralyzed with a neuromuscular blocking agent such as pancuronium bromide. Controlled hyperventilation is often used in an effort to decrease intracranial pressure. Cooling mattresses are used to keep body temperatures at normal range. Hypertonic glucose solutions given intravenously, as well as insulin, are often used.

Agents to reduce serum ammonia concentrations are also often used, the most common being neomycin sulfate or lactulose. The prothrombin time and other coagulation abnormalities may be corrected by administration of fresh frozen plasma. Exchange transfusion is used in some centers to correct various metabolic and hematologic abnormalities.

Intracranial pressure elevations are treated by administering osmotic diuretics, including mannitol, other agents such as glycerol or furosemide and controlling hyperventilation and muscular paralysis. Intracranial pressure is usually monitored by using intraventricular, subarachnoid or epidural monitors.

The role of high-dose barbiturates in the treatment of intracranial pressure elevations in Reye's syndrome[35] is somewhat controversial. Such therapy is effective in

reducing increased intracranial pressure, but may complicate the clinical course and slow the recovery.[36] Thus far, there is no convincing evidence that the outcome is improved substantially by the use of high-dose barbiturates.

Conclusions

Reye's syndrome is an acute, severe, metabolic encephalopathy occurring primarily in infants and children. The pathogenesis of the disorder is unknown, although a variety of environmental toxins have been implicated. Treatment is primarily supportive. However, with more aggressive therapeutic regimens that have been developed over the past ten years, the prognosis has improved considerably. Early reports[1] indicated a mortality of 80% to 90% in most series. Current mortality ranges between 10% and 40%.[4,34] Whether this is the result of more aggressive treatment, earlier diagnosis of the disease or the recognition of many milder cases is not clear. For whatever reason, many more patients survive the acute illness. For most of those children, the outcome is good.[37] They may return to completely normal function with no significant long-term neurologic disabilities. Early diagnosis and appropriate supportive therapy appear to be important in halting the progress of the disease and insuring a better outcome for these children.

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Specialty Conference

Recombinant DNA in Medicine

Moderator
STEPHEN D. CEDERBAUM, MD

Discussants
GEORGE C. FAREED, MD; MICHAEL A. LOVETT, MD, PhD, *and* LARRY J. SHAPIRO, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Associate Professor of Medicine.

Studies in bacteria and bacterial viruses have led to methods to manipulate and recombine DNA in unique and reproducible ways and to amplify these recombined molecules millions of times. Once properly identified, the recombinant DNA molecules can be used in various ways useful in medicine and human biology. There are many applications for recombinant DNA technology. Cloned complementary DNA has been used to produce various human proteins in microorganisms. Insulin and growth hormone have been extensively and successfully tested in humans and insulin has been licensed for sale. Mass production of bacterial and viral antigens with recombinant DNA technology is likely to provide safe and effective vaccines for some disorders for which there is no prevention. The cloned probes for the human α- and β-globin loci, for specific disease genes, such as the Z allele of α-antitrypsin, and for random genomic sequences are proving useful for prenatally diagnosing human genetic disorders and preventing their clinical consequences.

(Cederbaum SD, Fareed GC, Lovett MA, et al: Recombinant DNA in medicine—Interdepartmental Conference, University of California, Los Angeles [Specialty Conference]. West J Med 1984 Aug; 141:210-222)

STEPHEN D. CEDERBAUM, MD:* Seldom has a scientific or biomedical breakthrough evoked the awe, controversy or sheer incredulity that has accompanied the snowballing developments in the field of recombinant DNA technology or, more popularly, gene cloning and genetic engineering. Little more than one generation after Avery, McCloud and McCarty[1] showed that genes were encoded in DNA and Watson and Crick[2] interpreted the structure of these molecules, genes are being cut, manipulated and recombined to produce unprecedented insights in genetics and molecular biology and in the prospect of gene therapy. These developments have occurred not without anxiety to both scientists and nonscientists. Theologians and philosophers have discussed the dangers of altering human genetic makeup and even of producing human life in laboratories; environmentalists and politicians have raised fears of epidemics decimating the human race. Neither the most apocalyptic fears nor the most optimistic dreams appear to be imminent though neither is out of the question. Recombinant DNA technology has already had great impact in the fields of genetics,

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ABBREVIATIONS USED IN TEXT

AAT = α_1-antitrypsin
ADH = alcohol dehydrogenase
cDNA = complementary DNA
kb = kilobases

hematology, endocrinology, immunology and rheumatology, and shortly will forcefully impinge on the study of infectious diseases, neurology, orthopedics, oncology, cardiology and virtually every other area of medicine and biology.

The successful manipulation of genes requires that the following distinct processes be successfully accomplished[3]: (1) that DNA be cut in a predictable and reproducible way; (2) that two distinct pieces of DNA be combined in a controlled manner; (3) that an isolated piece of DNA be amplified millions of times, and (4) that the cloned gene or genetic material be identified.

A restricted host range for bacterial viruses has been known for many years. Beginning in 1952 several groups of investigators described the phenomenon of host-induced modification of the viral genome wherein the host range was dependent on the strain in which the virus was propagated.[4] In the early 1960s, Arber[4] showed that successful replication was accompanied by maintenance of the DNA in its intact macromolecular form, whereas failure of infection was characterized by the destruction of the intact viral genome. He predicted the existence of enzymes that hydrolyzed foreign nucleic acids after the recognizable host sequences were modified to escape attack by these proteins. In the early 1970s, Smith and Wilcox[5] described bacterial restriction endonucleases that destroyed foreign DNA but not that of the host *Hemophilus influenzae*. They and others have purified and described more than 200 such enzymes, most of which have absolute sequence specificity. One of these, Eco RI, an enzyme derived from an *Escherichia coli* R strain, recognizes a specific hexanucleotide sequence (Figure 1) and causes cleavage of the double helix in an unequal manner, leaving two 4-base fragments without their complementary, hydrogen-bonded partners. A given genome, or fragment thereof, will be cut into identical pieces each time it is subjected to the hydrolytic action of Eco RI or any other specific restriction endonuclease. The host genome is protected from the action of this enzyme by modifying the bases—for example, by methylation—so that the enzyme fails to recognize its normal sequence.

Figure 1 underscores the second feature of many restriction endonucleases that is vital to the task of genetic recombination, the generation of free single-chain base sequences that tend to form active hydrogen bonds with their complements. Two different DNA fragments can be hydrolyzed with Eco RI and, when mixed together and ligated enzymatically, form a new DNA molecule (Figure 2).

The third vital feature of a successful gene cloning is the duplication or cloning of an individual isolated piece of DNA, which is accomplished by inserting the foreign DNA into a bacteriophage or an autonomously replicating bacterial plasmid.

The existence of sexuality or the transfer of genetic information between different bacterial strains has been known and studied for more than 30 years.[6] In the 1960s, the rapid emergence of multiple drug resistance in bacteria led to the discovery of R factors, or autonomously replicating plasmids that can live with a bac-

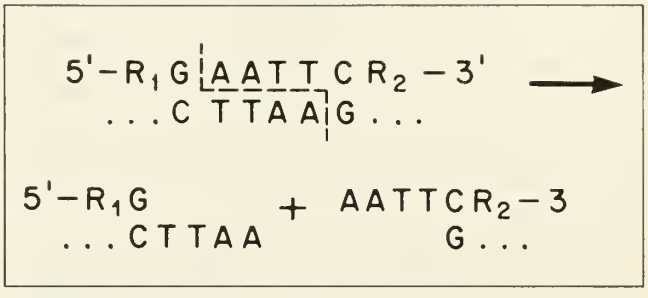

Figure 1.—The specific hexanucleotide sequence recognized by the restriction endonuclease Eco RI. R_1 and R_2 indicate the unknown flanking base sequences. The dashed line indicates the line cleavage of the double helix and the products are shown below, each with the 5′ cohesive end.

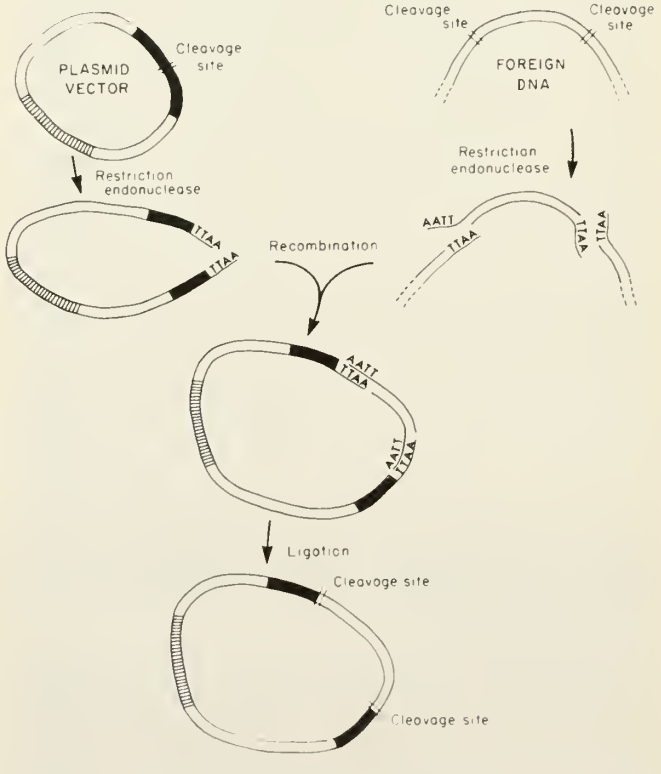

Figure 2.—Creation of a recombinant plasmid. The hatched areas represent a gene for tetracycline resistance and the dark areas for ampicillin resistance. After cleavage with Eco RI and reannealing, the foreign DNA is intercalated into the gene for ampicillin resistance.

terial cell and, in some instances, be induced to produce numerous copies.[7] This class of plasmids has been exploited as vectors for propagating unique pieces of DNA within bacterial cells (Figure 2). The plasmid may be cut with a specific restriction endonuclease and reconstructed with the foreign DNA inserted within the ampicillin-resistant locus, leaving the tetracycline-resistant gene intact. The recombinant vector is then introduced into the bacterial cell and the recipient selected by growth in the presence of an antibiotic. The recombinant plasmid may be identified by the loss of resistance to the second antibiotic, in this case ampicillin.

The gene-cloning procedure thus far described is not technically complex. In principle, one could produce a "library" of human DNA clones large enough to encompass the entire human genome. The library of individual clones would, however, be virtually useless. We would not have the faintest idea of the content of these clones and they could be used for little else save species identification, assuming they were reasonably species-specific.

A second limitation of the approach involves the nature of human genes and the use of cloned genes for protein production in bacteria. Genes for human proteins contain not only the DNA sequences that encode the amino acid sequence but also intervening sequences (introns), or base sequences intercalated in the coding regions, but not specifying a functional amino acid sequence. The introns are transcribed when messenger RNA is produced but must be excised before translation of mature RNA by the protein synthetic machinery.[8] Microorganisms do not have introns in their structural genes and lack the ability to excise them. Therefore, it is the sequence of mature message and not the gene that corresponds to the amino acid structural sequence of the protein product. To circumvent this problem, the DNA used for cloning is derived from messenger RNA or only the RNA actually transcribed in a specific tissue. The complementary DNA (cDNA) clone for phenylalanine hydroxylase would be found in a library from liver and not from spleen or pancreas.

The general scheme for cloning is shown in Figure 3. The messenger RNA is isolated from total RNA because of its polyadenylate tail and a complementary or cDNA chain is synthesized with the help of a reverse transcriptase. After separating the RNA-DNA hybrid, the second DNA chain is synthesized and, after suitable manipulation, is ready for incorporation into the plasmid vector.[9]

Isolating and identifying specific clones may be accomplished in various ways. This is the most difficult part of the cloning process and could, in some instances, require years. Various procedures have proved useful. The particular sequence in question can be enriched. Genes of the X chromosome can be obtained by isolating X chromosomes by differential cell sorting or by isolating a human X chromosome in a rodent

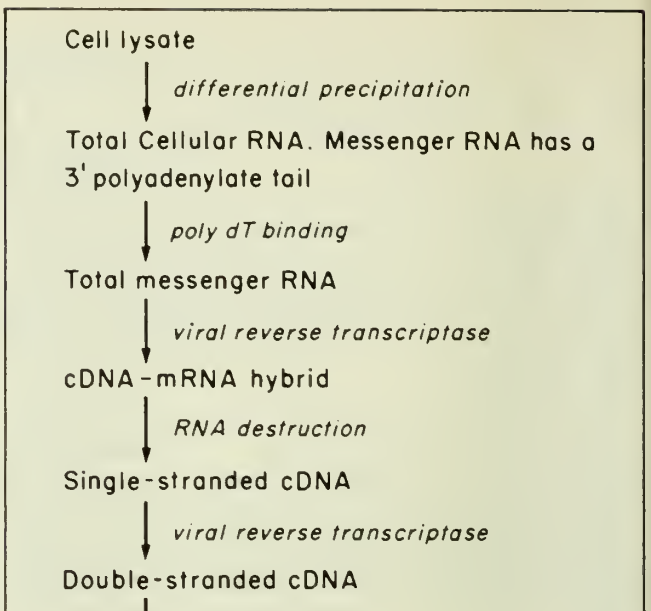

Figure 3.—Scheme of the important steps in cDNA production. cDNA = complementary DNA, mRNA = messenger RNA

host after cell hybridization.[10,11] Hemoglobin is isolated by using messenger RNA from reticulocytes, of which those for the α- and β-chain make up 90% of the total.[12] Rare messages can be enriched to near homogeneity using specific immunoprecipitation of ribosomes actively translating the protein.[13] The antibody recognizes the nascent chain and binds those ribosomes. The cDNA from these pools is greatly enriched for the desired protein. The metallothionein message may be greatly increased by growing cells either in culture or in animals in its heavy metal ligand, and the message further purified by size separation on a sucrose density gradient.[14] There are also strategies using principles similar to those noted.

The identity of a clone is proved ultimately by the congruence of its sequence and that of the RNA molecule or protein for which it codes. Because protein sequence information is laborious to obtain, indirect criteria are often applied. These generally require the availability of a monospecific or monoclonal antibody to the protein in question. Advantage is taken of the ability to translate messenger RNA in vitro, using most commonly a rabbit reticulocyte lysate. After antibody precipitation and polyacrylamide gel electrophoresis with sodium dodecyl sulfate, a radioactive band in the position of the molecular weight of the monomer of the protein in question is seen and is obliterated if excess cold antigen is added. The correct clone for the gene in question when denatured hybridizes with the complementary messenger RNA. This is assessed either by following the disappearance of the electrophoretic band from a whole cell messenger RNA preparation or

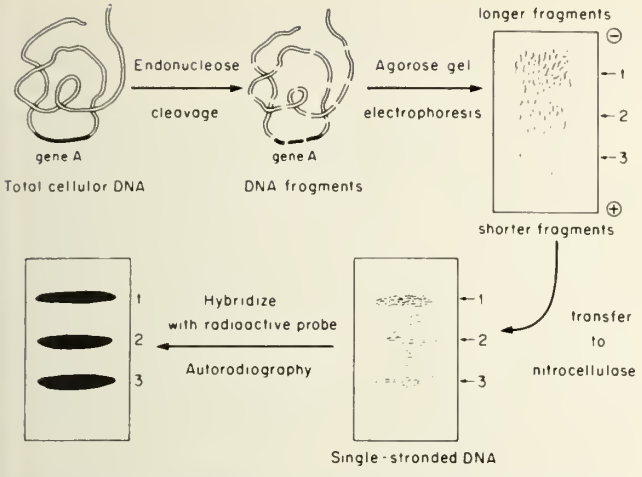

Figure 4.—Principles of the Southern blotting technique. After endonuclease cleavage and agarose gel eletrophoresis, the fragments of gene A are located at positions 1, 2 and 3, but cannot be seen against the background of random DNA fragments with a continuous size distribution. They are visualized with a complementary DNA probe rendered radioactive with ^{32}P, after hybridization and subjecting the nitrocellulose to autoradiography.

by its appearance after elution from the DNA and subsequent translation.[15]

Figure 4 shows the powerful technique by which genes complementary to a specific probe are recognized among random fragments of DNA. We now have a probe for human β-globin. To be useful, it must be able to identify and describe specific fragments of human DNA to which it is complementary. This is accomplished by obtaining whole cell DNA and cutting with one or another restriction endonuclease. When these random fragments are subjected to electrophoresis on agarose gel, they separate by size. When stained with ethidium bromide, a nonspecific DNA stain, we see a blur as the fragments distribute themselves continuously across the size scale. Dr Edwin Southern from Glasgow, Scotland, solved this problem.[16] The DNA is denatured and transferred from the agarose gel to nitrocellulose paper to which it is highly adherent. The probe rendered radioactive with ^{32}P is then hybridized to it. The radioactive band can then be visualized after autoradiography. A probe constructed chemically as a result of a known amino acid sequence can be used in this way to identify either fragments or clones on an agar plate.[17]

Protein Products of DNA Technology

GEORGE C. FAREED, MD:* Genetic engineering is a broad field encompassing classical types of genetic manipulation such as plant and animal breeding, human genetic counseling, conventional mutagenesis and somatic cell genetics. The techniques include chemical treatment of simple organisms such as bacteria, viruses, yeast and other lower organisms, selection of specific mutant phenotypes, fusion of cells in tissue culture to produce recombinant phenotypes, hybridoma antibodies and the dynamic field of recombinant DNA technology or gene cloning. Through recent advances in enzymology, bacterial genetics and nucleic acid chemistry, the DNA for specific genes can be chemically synthesized or physically isolated, such as those for peptide hormones and for antibodies and the interferons. It is possible to amplify them many thousandfold, determine their exact nucleotide sequences, locate entire structural genes and either chemically or biologically synthesize copies of these genes. Already, synthetic genes and cloned natural genes for many important substances, such as somatostatin, insulin, growth hormone, viral antigens and interferons, have been inserted into plasmids of bacteria and yeast that are capable of producing the functional product in abundant quantities.

Three broad classes of proteins are becoming products of the new biotechnologies: (1) enzymes; (2) hormones, such as growth hormone and insulin, which control various activities in different tissues of the body, and (3) some of the 100 or more molecules that make up the body's defense system against disease—such as interferon.

The dream of biotechnology is to turn the diversity of enzymes and other proteins to the benefit of humanity, designing an ideal microbe to make each desirable product. Many of these products can enhance the quality and length of our lives by their effects to counter infections, cancer, pain and aging. The specific goal of recombinant DNA for pharmacology is to produce in simple organisms such as bacteria and yeast, or possibly in farm animals, the multitude of human proteins and peptides that are physiologically beneficial. Most of these cannot be obtained for clinical use through other methods and their beneficial properties or uses cannot be evaluated until they are created through this technology.

Enzymes have evolved to catalyze the metabolism of virtually any raw material on earth. Enzymes turn sugars into alcohol and enable certain microbes to "mine" uranium and copper. There are 25,000 different species of microbe known, each with its own library of enzymes (though some enzymes are shared by many species).

Human Enzymes

The genes for several human enzymes or carrier proteins have been cloned and full-length cDNA recombined into bacterial or yeast plasmid vectors, permitting their synthesis in commercial amounts in the microbial cell. These include factors involved in blood clot formation or their dissolution, hydrolytic enzyme modifiers and albumin.

The potential usefulness of urokinase in fibrinolytic therapy for myocardial infarction and other conditions was recognized and studied more than a decade ago.[18] The plasminogen activators are present in small amounts in tissues and urine and the expense of puri-

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fication and their low abundance have made large-scale clinical studies difficult. Recently, investigators in the United States, Europe and Japan have cloned full-length cDNA for urokinase and other plasminogen activators and have achieved expression in microorganisms.[19,20] Genentech, Inc., is currently developing a clinical testing program for urokinase with its contractural partner, Grunenthal, Inc., in Germany. Commercially useful quantities of urokinase should be available by 1985.

Tissue plasminogen activator has become Genentech's fourth commercial product of genetic engineering technology, after interferon, insulin and human growth hormone. Dr Desire Collen of the University of Louvain, Belgium, purified small amounts of tissue plasminogen activator, an enzyme that dissolves fibrin and is produced naturally in the body; this led ultimately to its cloning and the creation of a bacterial expression vector for it.

Synthetic urokinase and tissue plasminogen activators will permit physicians to dissolve individual clots without causing the side effects common with anticoagulants such as heparin, which prevents the blood from clotting and can cause acute bleeding problems. This method of fibrinolysis is superior to that promoted by streptokinase as the proteolytic activity is restricted to the fibrin clot.

Liver proteins important in blood functions or transport of substances are being cloned and expressed in microorganisms. These include clotting factor IX,[21] fibrinogen,[22] albumin,[23,24] apolipoproteins[25] and α_1-antitrypsin. Among these, both albumin and α_1-antitrypsin have been produced in bacteria for clinical testing and large-scale production. The availability of "engineered" albumin will permit replacement with an osmotically active fluid without the risk of blood-derived products.

The recent cloning of the gene for human clotting factor IX[21] shows the power of recombinant DNA approaches to obtain the genes for proteins, which, compared with the genes for albumin, have few messenger RNAs. The production of complex proteins, such as clotting factors, which are normally glycosylated after their translation, may take place in yeast rather than in bacteria—which cannot do these posttranslational modifications—or in farm animals that have been genetically engineered to produce the human gene product.[26] Such progress raises the hopes that factor VIII may soon be produced and both factors VIII and IX become available in complete form for safe replacement therapy in cases of hemophilia A and B.

The gene for α_1-antitrypsin (AAT) has been cloned at the Zymos Corporation, Seattle, and its large-scale production was reported recently at the 11th International Conference on Yeast Genetics and Molecular Biology (Kyoto, Japan). α_1-Antitrypsin, normally produced in human liver and carried in the bloodstream, has been synthesized in ordinary bakers' yeast in a laboratory. α_1-Antitrypsin counteracts the effects of trypsin and perhaps other hydrolases produced by the body to destroy bacteria, air pollutants and cigarette smoke in the lungs. If insufficient AAT is produced by the body, the unneutralized enzymes may attack the lung tissue itself.

About 1 in 4,000 persons in the United States has severe, inherited AAT deficiency. These persons usually die prematurely of severe emphysema or liver disease.[27] About 1 in 20 persons in the United States is heterozygous and has a less severe deficiency. They too may be prone to pulmonary disease, especially if exposed to cigarette smoke or other unfavorable environmental pollutants.[28] The engineered product may be important in treating patients who have respiratory disease, whose bodies make insufficient quantities of the protein, and may prevent later disease if used preemptively.

The yeast cells selected for this genetic engineering ordinarily produce large quantities of alcohol dehydrogenase (ADH), an enzyme essential for normal growth. Zymos scientists have taken the promoter that triggers the production of ADH and attached it to the human DNA sequence coding for AAT. Thus, the yeast is tricked into producing the enzyme at any time it requires. The problems of safety will need to be examined in animals to assure that toxic or antigenic components of the yeast cell or growth media have been completely removed. Testing in animals to estimate the effective duration and inhibitory capacity of the protein also will be necessary. Long-term studies will be required to assure that the rate of deterioration in lung function has been stopped or substantially reduced. At present, no definitive treatment is known for illness caused by a genetic deficiency of AAT.

Although the initial clinical trials will be restricted to genetically deficient patients with emphysema, subsequent human trials may be extended to patients who have adult respiratory distress syndrome. Patients with this disease have abnormally low levels of AAT, and acute symptoms may be due partly to an excessive activity of an enzyme normally neutralized by AAT. Because adult respiratory distress syndrome is an acute rather than a chronic disease, the administration of AAT, if effective, would not require long-term studies to show its benefits.

Human Peptide Hormones

The second and most highly publicized family of products of recombinant DNA technology are the peptide hormones. These were the first substances produced in abundance and several have been subjected to successful clinical studies. The hormones include somatostatin (the first product of a synthetic gene),[29] human insulin,[30] growth hormone,[31] secretin,[32] calcitonin,[33] β-endorphin,[34] gastrin,[35] relaxin[36] and epidermal growth factor.[37] Small hypothalamic releasing factors, such as growth hormone releasing factor,[38] and newly discovered neuropeptides such as the calcitonin-related peptide important in limbic and cerebellar neural operations will be manufactured. Finally, many

growth and suppressor substances will become available and new therapies developed.

Somatostatin, the first biologically active human protein produced in bacteria, was made from a chemically synthesized cDNA, the sequence of which was deduced from the amino acid sequence, taking advantage of the universality of the genetic code.[29] Similarly, the first recombinant DNA product to be approved by the Food and Drug Administration, human insulin (Humulin) manufactured by Lilly, is produced in the same manner.[30] When the true sequence of the human gene was discovered, the functional artificial gene was found to differ in several codons for which degeneracy is present.

The bacterial production of insulin differs from that in humans in another important way. Whereas the insulin A and B chains are normally produced as a single molecule with excision of the connecting polypeptide after folding of the completed chain, the engineered A and B chains are produced in separate bacteria and combined in vitro. Human insulin is a little faster-acting than purified porcine insulin; in young patients who have diabetes a downward adjustment of the dose is necessary.[39,40] Immune reactions to human insulin have not been reported.

Bacterially produced human growth hormone also has been successfully tested in humans.[41] When commercially available in unlimited amounts, it will have a greater impact on medicine than insulin. Previously growth hormone was derived from human pituitary glands obtained at autopsy and was available in only limited amounts. Only patients with growth hormone deficiency could be treated and then often with doses that might have been suboptimal. The general availability of growth hormone also opens the door for possible abuse.

Protein Cellular Effectors

The final group of products produced in large amounts by recombinant DNA technology is the general class of proteins best described by the term cellular effectors. These include thymosin α_1,[42] the interferons and their hybrids[43,44] and, more recently, the prospect of producing numerous other lymphokines important for modulating the immune response, such as interleukin-2.[45]

The interferons have drawn the greatest amount of attention. They are small, heat-stable glycoproteins that have both antiviral and antitumor acivities.[46] When interferons are produced in bacteria, they are not glycosylated, but seem to retain biologic activity.[47] The results of the initial clinical trials with recombinant DNA interferon as an antiviral agent have been encouraging regarding the prophylactic treatment of rhinovirus infections and efficacy in hepatitis; cases of herpes infection are also being examined.[46] Although the antiviral activity of the interferons may prove most valuable clinically, they are also being examined for antitumor activity. In the first report[47] on a multidose phase I trial of leukocyte α-interferon from *E coli*, 81 patients with various refractory disseminated malignant lesions received injections of escalating amounts from 1 to 136 million units per injection. Toxic reactions were similar to those seen with nonrecombinant interferon—fever, chills, anorexia, nausea, vomiting, dose-dependent reversible leukopenia and serum aminotransferase elevations. Objective evidence of antitumor activity was seen in a small percentage of patients with tumor regression and remissions of as long as seven months, indicating that the genetically engineered product is biologically active. This tends to agree with smaller phase I trials for the treatment of osteosarcoma and Kaposi's sarcoma. Definitive assessment of the clinical efficacy of this and other interferons will await the results of phase II trials now in progress. Phase II cytoreductive studies in specific malignant neoplasms are under way to determine the frequency and duration of response with a maximum tolerated daily dose. Cloned interferons will probably be evaluated in many situations in which there is no therapy and a viral cause or immunologic disturbance has been noticed, such as in cases of multiple sclerosis and amyotrophic lateral sclerosis or even certain forms of arthritis.

When one looks at the contribution of DNA cloning technology to medical research on interferons, to other biologic response modifiers and to these various other protein products, all fields of medicine are certainly being profoundly influenced by this new evolving technology.

Recombinant DNA Products in Infectious Disease

MICHAEL A. LOVETT, MD:* The advances in antimicrobial therapy made in the past three decades have become the practical focus of the field of clinical infectious diseases. During the same three decades that followed the discovery of the double helical structure of DNA, advances in our basic understanding of microbial genetics have led to the creation of genetic engineering. Although recombinant DNA technology may increase the efficacy of industrially producing antimicrobial agents, it will be central to the next revolutions in the treatment of clinical infectious disease: new subunit vaccines and rapid diagnostic tools. In this review I will limit my discussion to the likely impact of recombinant DNA technology on preventing and diagnosing bacterial diseases. Similar considerations should be germane to viral, fungal and parasitic diseases.

The impetus for the use of recombinant DNA products in treating infectious disease arises from problems inherent in the use of native components of pathogens in diagnostic tests or vaccines. Bacteria may be difficult, or even impossible, to cultivate in vitro (such as *Mycobacterium leprae, Treponema pallidum*); the growth of large volumes of human pathogens (such as rickettsiae) can be dangerous; purification of microbial substances may be difficult, and the production of a desired substance by a pathogen may be unreliable. Contamination with undesirable pathogen-derived sub-

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TABLE 1.—*Likely Targets for Recombinant DNA-Based Vaccine*

Category	*Examples*	*Organism*
Cell surface proteins	Pili	*Neisseria gonorrhoeae, Escherichia coli*
	Outer membrane protein	Group B meningococci, *Hemophilus influenzae,* Group B streptococci
Toxins and virulence factors ..	IgA protease	*Neisseria, H influenzae*
	Enterotoxins	*E coli*
	Other toxins	*Clostridium difficile, Pseudomonas*
Polysaccharides	Kl capsular	*E coli*

stances is always a concern. Current recombinant DNA technology may overcome all the problems associated with pathogen-derived substances. Gene amplification and enhancement of gene expression in *E coli* or other bacterial hosts can cause the pathogen gene product to comprise a substantial fraction of the host cell mass, greatly facilitating purification and insuring stable production. It is safer to work with individual pathogenic gene products in *E coli* K12, in most cases, than with the native pathogenic bacterium.

Prospects for Recombinant Bacterial Vaccines

Human pathogenic bacteria are highly adapted to live in humans, and consequently the creation of effective antibacterial vaccines has been a formidable challenge. In some instances the ability of natural infection to confer long-lived immunity is in doubt (example: gonorrhea). Vaccines conferring reliable protection are available for only four pathogenic bacteria: meningococcal and pneumococcal vaccines consist of capsular polysaccharides and those for diphtheria and tetanus are inactivated bacterial toxins.

The study of pathogenesis has given us insight into the molecular basis of bacterial virulence factors. Recombinant DNA technology will not sufficiently control a bacterial disease unless key immunogens and virulence factors are defined and details of the host-parasite interaction are thoroughly understood.

Key bacterial surface proteins related to disease have generally shown great antigenic diversity. A classic example is the M protein of the group A streptococcus.[48] The M protein filaments protrude through the hyaluronic acid capsule and have an antiphagocytic activity that is critical to virulence. Immunization with an individual M protein confers lasting immunity. However, there are 55 antigenically distinct M protein types. This degree of antigenic diversity presents a difficult, but by no means insurmountable, challenge to recombinant DNA technology, as will be clear later in this discussion. Bacterial surface polysaccharides may also show antigenic diversity within a species (for example, pneumococcal capsular polysaccharides) and are often critical virulence factors or protective immunogens, or both.[49] Recombinant DNA technology has been most adept at enhancing expression of protein.

Targets for Recombinant Bacterial Vaccines

Likely targets for recombinant bacterial vaccines are listed in Table 1. The first group are the several varieties of bacterial surface proteins, among them the pili. Bacterial pili are filamentous, surface-located appendages that are polymers of polypeptide subunits. Pili are highly evolved to mediate attachment of bacteria to receptors on specific human tissues. In certain bacterial diseases, the presence of a special pilus-mediated attachment to a target tissue is critical to the virulence of the organism.[50]

To appreciate the potential of recombinant DNA to produce pili for human immunization, we must first consider important work with animals. K88 and K99 are designations for pili that mediate attachment of enterotoxic *E coli* to the small bowel of pigs and cattle, causing severe diarrhea. The genes for the pili have been cloned and expressed in *E coli* K12.[51] Expression of the cloned genes has been optimized and purified K88 and K99 subunit vaccines prevent diarrhea in animals (S. Falkow, PhD, verbal communication, 1982). This work is exciting for several reasons: It represents the first successful use of a recombinant DNA vaccine to control a bacterial disease. It also shows dramatically that parenteral vaccination with a subunit vaccine can result in effective immunity at a mucosal surface.

Enterotoxic *E coli* strains causing "traveler's diarrhea" possess special pili, designated CFA I and CFA II (for colonization factor antigens), that are critical virulence factors mediating attachment to human small bowel mucosa.[52] The CFA I and CFA II are therefore the analogues of K88 and K99 for human disease. It is reasonable to hope that the effective recombinant subunit vaccines based on CFA I and II may be created.

Bacterial strains causing pyelonephritis have special pili, called P pili, that bind to specific receptors of uroepithelial cells. These P pili have been cloned (G. Schoolnik, MD, and S. Falkow, PhD, verbal communication, 1982) and it should be feasible to learn whether or not P pili can form the basis of a human pyelonephritis vaccine.

Gonococcal pili mediate attachment to various human tissues and only piliated gonococci are virulent. The number of antigenically distinct gonococcal pili approaches that of group A streptococcal M protein types.[53] At present, the role of pili in immunity to the gonococcus is uncertain, but may be elucidated by structure-function studies of these pili (G. Schoolnik, MD, verbal communication, 1982). The gene for one serotype of gonococcal pili has recently been cloned in *E coli*.[53] As noted above, antigenic diversity of bacterial surface components critical to virulence is a problem that recombinant DNA technology must address. One

possible approach would combine the gene products of well-defined antigenically diverse determinants of type-specific immunity together into a polyvalent vaccine, much as may now be done using conventional approaches.

Other surface proteins in addition to pili are under consideration as candidates for experimental vaccines. Outer membrane protein of group B meningococci, type b *Hemophilus influenzae* and group B streptococci will be studied as adjuncts or alternatives to capsular polysaccharide.[54] Gonococcal[55] and chlamydial[56] outer membrane proteins may also contribute to protective immunity.

The second group of candidates for engineered antigens to serve as antibacterial vaccines are virulence factors and toxins. Pathogenic *Neisseria* and *H influenzae* produce an IgA protease whose role in disease has been unclear. The genes for these proteases have been cloned and expressed in *E coli* and genetic systems for their reintroduction to the species of origin have been established (S. Falkow, PhD, verbal communication, 1982). Genetic manipulation of IgA protease genes should facilitate an understanding of their role in the pathogenesis of disease.

Bacterial exotoxins represent another area where recombinant DNA technology has had an impact both in the understanding of basic pathogenic mechanism and by offering vaccine potential. The gene for the heat-labile toxin of enterotoxic *E coli* has been cloned and sequenced.[57] The genes specifying attachment and toxic activity have been defined, permitting construction of a vaccine comprised only of the binding subunit.

It should be possible to clone several medically important toxins, such as those elaborated by *Clostridium difficile, Pseudomonas,* the erythrogenic toxins of streptococcal and staphylococcal strains and other toxins associated with food poisoning. With a cloned gene, structure-function studies can be done that could separate toxic from immunogenic portions of the molecule, leading eventually to "toxoid" vaccines in which the toxic moieties have been genetically deleted.

The final vaccine candidates I will describe are the capsular polysaccharides. *E coli* capsular antigen K1, which is immunochemically identical to the capsule of group B meningococcus, is associated with many *E coli* strains causing meningitis. Using cosmid cloning, Silver and associates[58] transferred the gene(s) specifying K1 biosynthesis to unencapsulated *E coli* K12 laboratory strains. This represents the first use of recombinant DNA to study capsular polysaccharides.[58]

In my laboratory we have cloned a 2.1-kilobase (kb) segment of *Treponema pallidum* DNA that directs the synthesis of a protease-resistant periodate-sensitive molecule. We have isolated an identical molecule from *T pallidum.* The cloned antigen reacts specifically with serum from patients who have had syphilis. It is highly immunogenic for rabbits and induces the formation of antibody that immobilizes virulent *T pallidum* in vitro (T. Fehniger, A. Walfield, PhD, and M. A. Lovett, MD, PhD, 1983, unpublished data). Vaccination experiments are now in progress for experimental syphilis.

Synthesizing cell surface polysaccharide from pathogenic bacterial species may be important for several reasons. Stable and abundant production of antigen can be achieved without the difficulty or the potential bio-hazard inherent in cultivating large volumes of a fastidious or noncultivatable pathogen. There is also the potential to engineer genetically the enzymes involved in polysaccharide synthesis so that polymers of altered composition and antigenicity can be created.

Recombinant DNA in Diagnosing Infectious Disease

Using cloned genes for *E coli* heat-labile enterotoxin, Moseley and co-workers[59] have shown that DNA hybridization is a powerful tool to detect the presence of a pathogen directly in clinical specimens. "DNA probes" have been constructed that detect *Chlamydia trachomatis, N gonorrhoeae* and a variety of enteric pathogens (S. Falkow, PhD, verbal communication, 1982). DNA hybridization has been used to detect cytomegalovirus DNA in urine.[60]

Because certain genes encoding antimicrobial resistance can be readily cloned, DNA probes will probably identify a pathogen and will also show its antimicrobial resistance. DNA probes could also be used as a rapid diagnostic adjunct to tissue culture or conventional bacterial culture techniques. Before DNA probes can be routinely used in clinical microbiology laboratories, however, methods of labeling the DNA must be developed to avoid the use of radioisotopes. The hybridization itself can be done in less than three hours.

Recombinant DNA technology can provide large quantities of pure microbial antigens for accurate and reproducible serotesting. The cloned antigens may be used directly in the serotests; they could also be used in monoclonal antibody-based tests. A *T pallidum* antigen synthesized in *E coli* has been a better serodiagnostic antigen for diagnosing syphilis than conventional and treponemal tests (M. A. Lovett, MD, PhD, 1983, unpublished data).

Applications of Cloned Genes

LARRY J. SHAPIRO, MD:* Almost immediately after the discovery that recombinant DNA techniques could be applied to eukaryotic and mammalian systems, intense interest developed in the possible application of these methods to several vexing problems in clinical medicine.[61-63] The fact that these capabilities have come into being as the fields of medical genetics and prenatal diagnosis are moving into their adolescence has assured an enthusiastic reception for the attendant new ideas and concepts in this sector of medical practice. At present, although applications of recombinant DNA technology to clinical genetics are relatively limited in a technical sense, there are few workers in this area who have not been gripped by the intense excitement and sense of optimism that has come about as a result

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of the first few forays into this new arena. In the hope of sharing some of that excitement, I will review briefly some recent developments and strategies involving the application of this technology to genetic counseling, prenatal diagnosis and eventually to the treatment of inherited diseases.

Prenatal diagnosis is now a well-established discipline that has developed around techniques of fetal visualization (such as ultrasound, fetoscopy and radiography), the biopsy of fetal tissues and the analysis of amniotic fluid and its cellular constituents.[64] Cultured amniotic fluid cells have been widely used for prenatal detection of chromosome defects and inborn errors of metabolism. Biochemical diagnosis depends, however, on a relatively precise knowledge of the nature of the genetic defect in question, on the normal expression of the function in question in relatively undifferentiated amniotic fluid cells and on normal levels of expression of this function to an extent that the analysis of the number of cells obtained after a few weeks of growth in culture can be carried out relatively rapidly in the second trimester of pregnancy.

The use of suitable cloned probes for diagnosing genetic defects by direct analysis of fetal cellular DNA promises several advances in this process. First and most important, the primary genetic abnormality can be examined directly. Expression of a detectable cellular phenotype is not required and therefore one is not limited to the repertoire of inherent responses of amniotic fluid cells. The examination of globin genes or genes related to liver-specific proteins becomes possible even though the cells to be studied do not produce globin or liver proteins. Second, the possibility of detecting prenatally conditions in which the primary genetic defect is unknown or uncertain becomes tenable through genetic linkage analysis. This strategy is not completely novel. Initial results using recombinant DNA-generated markers suggest that the high degree of variability or polymorphism, which will be detectable throughout the human genome using suitable molecular probes, will logarithmically enhance our capabilities to deal with new diseases both by genetic counseling and by prenatal diagnosis. Finally, the technical nature of the procedures involved should make possible more rapid laboratory diagnosis using materials other than just growing and dividing amniotic fluid cells. Direct analysis of the DNA of uncultured cells is possible. In addition, attention has been directed recently toward the use of transcervical chorionic villus biopsy to obtain tissue suitable for fetal DNA analysis during the first trimester of pregnancy. Thus, the duration of maternal anxiety, the medical risk of pregnancy termination and psychosocial concerns related to midtrimester abortion can all be abated.[65,66]

The requisites for detecting any given disease at a genomic level are the availability of a suitable cloned probe for the gene in question and a detailed knowledge of the molecular nature of the defect for which the fetus is at risk. The only clinical experiences reported to date involve disorders of the human α- and β-globin loci, which are due to the early availability of probes for these regions of the genome and the high frequency with which clinically significant disorders involving these genes are found in human populations. Experience with these conditions will serve as a prototype for other diseases.

Many patients with α-thalassemia and some patients with β-thalassemia or $\delta\beta$-thalassemia seem to have actual deletions of genetic material involving all or part of the relevant chromosomal regions. Such defects can be detected by molecular hybridization with suitable probes either in solution or on Southern blots.[67,68] The interpretation of such experiments is quite straightforward as homozygous affected subjects would be missing an entire band corresponding to the deleted gene sequence.

Although many heritable diseases may be the result of gross deletions, several other conditions have resulted from smaller alterations of the genome. Single-base changes may result in amino acid substitutions in the structure of a protein affecting either the function, stability or location of the gene product. In addition, small deletions, mutations producing early termination of protein elongation and frame-shift mutations leading to complete alteration of the gene product have all been described in mammalian systems. Furthermore, the relatively recent recognition of intervening sequences (introns) described by Dr Cederbaum suggests new possibilities for the genesis of hereditary disorders. The complexity of the pathway of maturation of messenger RNA, including splicing out of the introns from primary transcripts, polyadenylation at the 3′ end of messenger molecules and the addition of a translation site at the 5′ end before transport from nucleus to cytoplasm, suggests a host of other possibilities for mutations to interfere with the production of normal amounts of protein; these gene products are of normal structure and function though quantitatively reduced. Indeed, the study of the numerous thalassemia mutations in humans has, by their disruption of globin synthesis, provided the most detailed information on these processes.

To provide potentially useful diagnostic information in instances of this type, detailed information is required about the molecular lesion in the specific defect for which the person in question is at risk. In patients with well-documented sickle cell disease, a single A to T base substitution in the middle position of codon 6 changes the specified amino acid from glutamic acid to valine. This defect may be present in most sickle hemoglobin genes. However, as discussed previously, the molecular defects in the thalassemias are very heterogeneous and are the result of a wide spectrum of genetic alterations. It is therefore necessary to be able to study the relevant mutant gene in either a heterozygous or homozygous state before attempting prenatal diagnosis. Certain disorders, like sickle cell disease in blacks or Tay-Sachs disease in Ashkenazi Jews, may turn out to be less heterogeneous, but many

other defects, even those with very similar phenotypes, will show a great deal of molecular variability.

There are presently two strategies that should be widely applicable for the detection of discrete genetic defects by molecular hybridization techniques. These involve the use of synthetic oligonucleotide probes and the use of site-specific restriction endonucleases to identify alterations in cellular DNA. A recent example of the use of synthetic oligonucleotide probes has been provided by workers at the City of Hope Medical Center (Duarte, California).[69] They have chemically synthesized two probes that correspond to 19 bases of the β-globin sequence. The probes were identical except at a single position corresponding to the alteration in the β^S-globin gene. By controlling conditions of hybridization of such radioactively labeled probes with great care, specific hybridization of each probe with its homologous gene was obtained. The considerable technical advances in synthetic oligonucleotide chemistry make it plausible to generate such probes where any specific single nucleotide substitution in a mutant gene has been identified. However, this specific knowledge will be needed and exquisite care in the control of the temperature and conditions of hybridization may limit the widespread applicability of such methods. Finally, the specific nature of the nucleotide substitution examined will alter the relative stabilities of properly matched and mismatched hybridization between probe and cellular DNA.

An approach to prenatal or postnatal diagnosis by analysis of genomic DNA that may be more general makes use of the site-specific restriction nucleases described earlier in this conference. About 200 restriction enzymes with various specificities have been isolated and characterized.[70] With the knowledge of a specific nucleotide sequence alteration in a given genetic disorder, it should be possible to search through the known restriction enzymes and find one such reagent whose recognition site would be destroyed or an alternate site created by the mutation in question. After digesting a patient's DNA with the relevant enzyme and locating by electrophoresis specific fragments on Southern blots with labeled probes, size and hence electrophoretic differences between mutant and normal genes should be uncovered. Several technical requisites are necessary, however, before such a strategy may be used. These include the use of appropriate probes, the identification of enzymes that generate restriction fragments, which differ sufficiently in length in mutant and normal genes, and careful control of reaction conditions to ensure complete digestion of the DNA. A final problem is the possible pitfall of restriction site polymorphism unrelated to the mutation in question, which could confound the Southern blot analysis. There is substantial, benign variation in nucleotide sequence from one person to another; some of this variation might occur close to the site being studied, causing erroneous interpretation of results. Effective restriction enzyme tests for sickle cell disease have now been reported based on the use of Dde I or Mst II, with the latter enzyme being more generally useful.[71,72] Mst II cleaves at the sequence CCTNAGG, where N is any nucleotide. This sequence is included in normal β-globin genes (CCTGAGGAG) but not in a β^S-globin gene (CCTGTGGAG). A sickle gene, therefore, will not be cut at this position and a longer gene fragment results.

Much attention has been given recently to the use of benign restriction endonuclease site polymorphism as genetic markers to provide counseling and diagnostic information to families at risk for genetic disorders of as-yet-uncertain causes. This approach is predicated on the use of family linkage data and gene mapping technology reviewed recently by Sparkes and colleagues.[73] The use of DNA analysis in such endeavors is not fundamentally different from the use of any other genetic markers; the DNA polymorphism, however, should be more readily detectable, giving rise to more recognizable variability at more locations throughout the genome.[74]

At least three significant limitations are inherent in this strategy. First, because one is using a linked polymorphism as a genetic marker, by definition that marker lies at some measurable distance from the mutant gene whose transmission is to be studied in a pedigree. There is, therefore, a finite probability that the polymorphisms and the gene of concern will be separated from one another by recombinational events. The second limitation is based on the fact that no matter how frequently one observes variability at a given polymorphic region, some subjects in pedigrees will not be informative about transmission of presumably linked genes. This problem obviously diminishes with increasing numbers of polymorphisms detectable in the same region. For example, a single variant at a genetic locus present in less than 10% of the population will not be terribly useful for linkage studies. The same variant, if present in 50% of the genes in a population, will be much more useful but many people (half) will be homozygous for one or the other variant and thus uninformative about transmission of genes to their offspring. A single genetic locus or region with many different alternative alleles present in the population at relatively high frequency, as best typified by the human leukocyte antigen region, provides the best situation for linkage analysis. Third, the main deterrent to the use of linkage analysis is the need to do relatively complete family studies for each diagnostic procedure. This is necessary to establish the phase relationship of the mutant gene and the marker in each pedigree. Despite these limitations, linkage analysis is increasingly being done as the only reasonable means presently available to provide diagnostic information to families at risk for disorders such as pseudohypertrophic (Duchenne) muscular dystrophy, Huntington's chorea or cystic fibrosis where few clues to the primary genetic defects are available.

Two types of probes have been used in attempts to identify usefully polymorphic linkage markers: (1) probes for genes already cloned and of known func-

tion, and (2) quasi-random cloned fragments of DNA of unknown function but whose location in the genome can be determined and whose genes show polymorphism as an "anonymous sequence." A substantial amount of effort has gone into identifying polymorphic restriction sites near the β-globin locus, which has proved useful for the study of mutations leading to hemoglobinopathies and thalassemias. One of the first such polymorphisms identified was the absence (or presence) of an Hpa I restriction site in the 3′ flanking DNA of the β-globin gene.[75] This polymorphism results in Hpa I-digested DNA that contains the β-globin gene in a 7,600 base-pair fragment (7.6-kb) or in a 13,000 base-pair (13.0-kb) fragment depending on whether the recognition site is present or absent. Kan and Dozy[75] found that most, but not all, β^S-genes were associated with a 13.0-kb fragment and most β^A-genes were associated with a 7.6-kb fragment. If family studies were done to verify the phase relation of the restriction fragment polymorphism and the β-gene, the former marker could be used for the prenatal diagnosis of sickle cell disease. Subsequent work by several groups has identified numerous other linked polymorphisms in the β-globin region, which should be increasingly useful for the diagnosis of defects in this portion of the genome, especially in relatively inbred populations.[76-78]

By analogy, random cloned fragments of DNA from other regions of the genome should also be useful if they show significant polymorphisms.[79] Such probes need not be derived from any functional gene but must represent unique sequences within the genome. Some DNA sequences are repeated several or even thousands of times in the genome. Segments of DNA to be used to search for polymorphism must represent discrete genetic loci. One of the several strategies used to identify such probes is chromosome isolation, either physically[10] or in somatic cell hybrids.[11] Such chromosome-specific DNAs can be regionally mapped in the standard gene-mapping fashion using hybrid cell panels derived from patients with translocations. Once such probes are located, polymorphism can be sought using a reasonable number of test subjects and a variety of restriction endonucleases. Finally, linkage with a specific disease gene can be sought by studying multigenerational families, segregating both the DNA polymorphism and the disorder in question. An example of such application is the work of Davies and associates[80] in identifying a probe from the short arm of the X chromosome, which has a polymorphic restriction site nearby and appears linked to the locus for pseudohypertrophic muscular dystrophy. Although these results are preliminary and the genetic distance involved is too great to be of clinical use, studies such as these point the way toward developing a high-resolution map of the human genome based on these polymorphisms. This map would permit genetic counseling and prenatal diagnosis even for disorders whose cause is unknown.

In addition to these diagnostic implications, molecular technology will surely improve the therapeutic approach to genetic diseases. The use of recombinant DNA methods to generate protein products is being investigated. Some of these products, however, could be enzymes, or growth factors, that various patients might be missing on a genetic basis. For example, numerous clinical trials have been reported of enzyme replacement therapy for lysosomal storage diseases. However, most of these experiments have been impeded by the lack of a ready and available supply of human enzyme. Such a source of enzyme might eventually be found in bacterial production systems.

Of more long-range applicability is the direct insertion of genes into mammalian cells and even into whole organisms. There are two conceptually disparate approaches. The first involves introducing functional genes into individual somatic cells of a patient, probably in vitro, and then returning these engineered cells to the patient. The second approach involves introducing new genetic information to all of a person's cells, including germ cells, which would thus involve a true genetic change that could be transmitted to progeny. These two approaches differ from each other in technical difficulty and certainly in moral and ethical content. Although the technical capacity to introduce genes either into cultured cells or into fertilized mouse zygotes is clearly at hand, procedures to ensure site-specific integration into the genome and appropriately regulated expression are not yet available. Nonetheless, Cline and co-workers[81] have reported transferring dihydrofolate reductase genes to murine bone marrow cells and selecting methotrexate-resistant recipient cells in intact animals. Several laboratories have introduced cloned genes by microinjection into fertilized mouse eggs and detected the integration, transmission to progeny and expression of these genes.[82-88] Perhaps the most dramatic experiment reported to date involves the introduction of a cloned rat growth hormone gene (linked to a metallothionein promoter) into such mice.[26] This resulted in animals that had as much as 800 times normal levels of circulating growth hormone and that achieved twice the size of their normal littermates.

Clearly, the advent of recombinant DNA techniques and their application to biology and medicine has ushered in one of the most exciting eras of human intellectual endeavor. Although many technical and conceptual barriers remain, there is clear promise to improve the outcome for families affected by genetic diseases through better diagnosis, counseling and treatment.

Summary

DR CEDERBAUM: *We have reviewed some of the basic principles of recombinant DNA technology and some areas of extant or imminent impact on clinical medicine. We believe that the true potential of this technology has just begun to be exploited and that it is reasonable to anticipate major strides in the next few years. These advances will be felt in the production of new and more useful biologics and drugs; in the de-*

velopment of probes providing a deeper understanding of normal function, including that of development of the immune system; in the understanding of gene expression in embryologic development and maturation, and in the existence, nature and control of "oncogenes" that may play a role in cancer. Ultimately cloned genes, or their complementary DNA, will be introduced and expressed in foreign cells in a predictable and reproducible way and serve as the basis for gene therapy. We are confident that involvement of recombinant DNA technology will increase at the forefront of medicine.

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Medical Staff Conference

Antithrombotic Therapy for Pulmonary Embolism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Each year we are privileged to have a Medical Staff Conference given by each of the chief medical residents who are completing four years on the house staff here at the University of California, San Francisco (UCSF). This is such an occasion.*

Dr Seth Landefeld received his undergraduate degree from Harvard and then spent two years as a Rhodes Scholar at Oxford. He then returned to this country to complete his medical education at Yale. Seth will be leaving UCSF to begin training as a fellow in the Division of General Internal Medicine and Primary Care at the Brigham and Women's Hospital in Boston. We greatly appreciate the leadership and dedication he has brought to our training program.

DR LANDEFELD:† Few diseases threaten the lives of our patients as dramatically or challenge our diagnostic acumen and therapeutic ambitions as keenly as does pulmonary embolism. This challenge is no small matter, especially because we commonly believe pulmonary embolism is one of those rare phenomena in medicine, a life-threatening disease that can be cured with specific therapy. Harry Zilliacus, a Swedish pioneer of the use of heparin, stated the case for antithrombotic therapy in 1946: "Thromboembolism can be as effectively combated with heparin and, where it can be applied, with dicumarol, as pernicious anemia and diabetes mellitus with their specific agents."[1]

This therapeutic imperative inspired a search for better diagnostic agents. In the past 20 years lung scanning and pulmonary angiography have enabled accurate premortem diagnosis.[2,3] New, less invasive techniques, such as digital subtraction angiography, may soon provide diagnostic information as accurately as does traditional angiography.[4] The accepted treatment of pulmonary embolism, however, has seen few recent advances; heparin and coumarin derivatives remain the standard of care, as they were in the 1950s, and the role of thrombolytic therapy remains controversial.

I will examine the role of antithrombotic therapy—that is, the use of heparin, coumarin derivatives or thrombolytic agents—for treating acute pulmonary embolism, but will not discuss other syndromes of pulmonary thromboembolic disease, primary prophylaxis or surgical management.

I chose this topic for three reasons. First, antithrombotic therapy for pulmonary embolism is not well founded on experimental or clinical data, though it certainly is strongly supported by tradition. Second, antithrombotic therapy may often be toxic. Clearly, knowing both the efficacy and the toxicity of these agents can guide us in their best clinical use. Finally, recent investigations suggest new medical therapies that may be both safer and more effective.

Pathophysiology

Pulmonary embolism has two major clinical manifestations, acute respiratory and circulatory insufficiency. Experiments on animals and clinical observations have shown that, in general, the bigger the embolus, the more dramatic are the acute manifestations. The cardiopulmonary effects of acute pulmonary embolism, however, are often greater than can be accounted for simply by the degree of mechanical occlusion of pulmonary vasculature.[5,6] If mechanical obstruction of pulmonary blood flow were the only effect of embolism occluding less than 50% of the pulmonary vasculature, such submassive embolism would

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ABBREVIATIONS USED IN TEXT

TPA = tissue-type plasminogen activator
UPET = Urokinase Pulmonary Embolism Trial

lead only to an increase in physiologic dead space and alveolar hypoventilation. Patients with submassive embolism, however, often have hypocapnia due to alveolar hyperventilation, hypoxia reflecting an increase in physiologic shunt and sometimes an increase in pulmonary vascular resistance.[7] Similarly, massive embolism occluding more than 50% of the pulmonary vasculature often leads to more dramatic physiologic and clinical consequences than can be accounted for on the basis of mechanical obstruction alone. For example, reducing the pulmonary vascular surface 50% by pneumonectomy rarely leads to pulmonary hypertension, whereas a similar degree of vascular obstruction by embolism often does.[7,8]

Such observations suggest that neurohumoral responses contribute to the cardiopulmonary effects of pulmonary embolism. In fact, the idea of influencing such hypothetic neurohumoral responses led to an early report of a strikingly successful therapy. Investigators in 1940 reported 18% mortality in 22 patients with pulmonary embolism treated with atropine, papaverine hydrochloride or both, in contrast to 87% mortality in 100 untreated patients.[9] Unfortunately, the use of only this regimen has not been supported by the experience of others.

Several recent studies suggest that platelet secretions may play a major role in determining the acute responses to pulmonary embolism. In dogs, for example, experimental pulmonary emboli led to an increase in thromboxane—a prostaglandin with vasoconstrictor properties—that correlated with increases in physiologic shunt, pulmonary vascular resistance and dead space.[10] The concomitant fall in the dogs' platelet counts suggests that thromboxane was released by platelets depositing on the embolus. Pretreatment with imidazole, a thromboxane synthetase inhibitor, or with indomethacin, a cyclooxygenase inhibitor, prevented the rise in thromboxane and limited the changes in shunt, dead space and vascular resistance without affecting the fall in platelet count. Therefore, the effects of imidazole and indomethacin are likely due to decreased platelet release of thromboxane. Infusion of prostacyclin, a vasodilatory prostaglandin, had similar beneficial effects. In a rabbit model, pretreatment with as little as 5 mg per kg of body weight of aspirin has shown similar dramatic effects: pretreatment decreased the mortality from 40% to 0% and even averted hypotension.[11] The evidence suggests, then, that the cardiopulmonary effects of acute pulmonary embolism may be due to the secretions of platelets involved secondarily in the embolus as well as to the consequences of mechanical obstruction by the embolus itself.

Natural History

The question of natural history, What happens to the embolus and to the patient after the acute event?, cannot be answered fully as adequate studies have not been done. A review of relevant experimental, clinical and epidemiologic data may be helpful, though, on the premise that in the land of the blind the one-eyed man is king.

Experiments in animals show that fresh pulmonary emboli generally resolve rapidly. Moser and co-workers, for example, have shown that in dogs, fresh pulmonary emboli dissolved spontaneously to less than half their original volume three hours after embolization and to less than a third the original volume in six hours.[12] The degree of spontaneous thrombolysis differed greatly among animals, however, from 0% to 90% reduction in clot volumes at three hours. These and other similar results[13] underscore the importance of controlled experiments in evaluating thrombolysis and also suggest that there may be great variation in the rate of endogenous resolution of pulmonary emboli.

Our understanding of natural history should not rely too heavily on animal models for several reasons. Most important, people in whom pulmonary emboli develop may have a systemic rather than just a local predisposition to thromboembolism; perhaps the apparently gradual resolution of emboli in patients treated with antithrombotic agents indicates such a difference. Second, clinical pulmonary emboli may be different—perhaps older and less susceptible to thrombolysis—from the fresh thrombi studied in many animal models. There may also be species-specific differences in fibrinolysis.

Clinical studies give little information about the spontaneous resolution of pulmonary emboli. One patient, a 57-year-old man who suffered emboli to bilateral segmental pulmonary arteries, was not anticoagulated and had serial pulmonary angiograms.[14] This man's emboli completely resolved within seven days of the diagnosis, but this remains an isolated clinical report.

Epidemiologic data are more plentiful but no more definitive. The notion that 30% of patients with untreated pulmonary embolism will die is commonly held on the basis of an argument outlined by Dalen and Alpert in 1975.[15] To establish the mortality rate of untreated pulmonary embolism as around 30%, they cited five series in which the mortality rate of patients with untreated pulmonary embolism ranged from 18% to 35%. However, several problems invalidate this review as a method for establishing a firm estimate of the rate of untreated pulmonary embolism. First, review of a larger number of reports of untreated pulmonary embolism (Table 1) shows such a broad range of mortality rates—from 0% to 91%—that one must be skeptical of either pooling data or choosing one study over another unless its methodology is clearly superior. None of the studies required angiographic or lung scan

evidence of the diagnosis. Second, the criteria for selecting cases in many of the series may have biased the results. Many studies, including two of the five cited by Dalen and Alpert,[18,19] included cases in which the diagnosis of pulmonary embolism was made only at autopsy. Some series reported as untreated those patients who had contraindications to anticoagulation and thus may have been sicker than treated patients.[20] Third, the therapeutic standard before the introduction of antithrombotic therapy was prolonged and strict bed rest, which itself may have been detrimental. In summary, the data on the mortality rate of untreated pulmonary embolism are neither consistent nor reliable.

A key issue is that of recurrence: Does a pulmonary embolus herald fatal or debilitating emboli in the future? The answer to this question, too, is unclear (Table 2). Although there is a consensus that many patients (25% to 71%) with fresh pulmonary emboli found at autopsy have evidence of old embolism, this finding cannot lead to an estimate of the risk of recurrence in the living. The reports of recurrence rates after an initial clinical diagnosis of pulmonary embolism vary so widely that they are of little help. Although similar methodologic flaws mar these studies, disparities in the patient populations studied probably explain some of the differences. The lowest recurrence rates occurred among patients with total hip replacements, whereas the highest mortality rates occurred among those with heart failure or serious contraindications to anticoagulation.[18,20,21]

Antithrombotic Therapy

In 1938 heparin was reported as the first drug used for the antithrombotic treatment of pulmonary embolism.[25] This new treatment was rapidly and enthusiastically accepted, possibly reflecting William Osler's adage that "the desire to take medicine is perhaps the greatest feature that distinguishes man from animals."[26] The use of heparin was embraced, however, not only because of human nature but also because of the results of clinical trials and the belief in the then-current theory that endogenous heparin bound to prothrombin was an important check on coagulation. Thus thromboembolism was viewed as a deficiency disease analogous to pernicious anemia and heparin was viewed as the specific therapy.[1]

Although this appealing theory has been discredited, heparin may have several beneficial effects. Heparin is not itself thrombolytic but it has been shown to allow more rapid dissolution of pulmonary emboli in Moser's dog model (66% dissolution at three hours in treated animals and 52% dissolution in untreated animals).[12] By various mechanisms, including the potentiation of antithrombin III and the inhibition of platelet deposition, heparin may also prevent the extension of pulmonary emboli, the extension or recurrence of underlying venous thrombosis, platelet release of serotonin and bronchospasm.[27,28] The clinical importance of these experimental results, however, is unknown. Coumarin derivatives probably act only by inhibiting the synthesis of functional factors II, VII, IX and X.

Does anticoagulation affect the course of patients with pulmonary embolism? One would certainly think that it should, but let me say at the outset that I do not know the answer. I will approach the question first by summarizing several large series of patients treated with anticoagulants during three eras (Table 3). In the first decade of anticoagulant therapy, three large series had a combined mortality rate of 0.2%, in contrast to mortality rates of 5% in four large series gathered during the next 25 years and 9% in heparin-treated patients in the multicenter Urokinase Pulmonary Embolism Trial (UPET).

It is difficult to explain a nearly 50-fold increase in mortality, and one has to wonder why the results of anticoagulant therapy appear to have worsened so dramatically. Could we have lost our therapeutic knack?

TABLE 1.—*Mortality of Untreated Pulmonary Embolism*

Number of Series	*Years*	*Number of Patients*	*Mortality Percent (Range)*	*Reference Numbers*
13*	1903-1940	2,478	34 (13-91)	1 (cited in)
5	1941-1961	551	35 (2†-51)	1,16,17,18,19
2	1962-1977	327	2.5(0-42)	20,21

*These series include cases of sudden death due to pulmonary embolism.
†Based on a review of case reports in Zilliacus.[1]

TABLE 2.—*Recurrence of Pulmonary Embolism in Patients Not Treated With Anticoagulation*

Series	*Number of Patients*	*Fatal Recurrence Percent (Range)*	*Nonfatal Recurrence Percent (Range)*	*Reference Numbers*
Clinical (1960-1967)	453	9.7 (0-35)	9.5 (3.2-26)	17,18,20,21
Autopsy (1941-1968)	279	48 (25-71)	...	22,23,24

TABLE 3.—*Results of Treatment of Pulmonary Embolism With Anticoagulation From Different Eras*

Series	*Number of Patients*	*Mortality Percent*	*Total Recurrence Rate Percent*	*Reference Numbers*
Early (1937-1947)	581	0.2	2	1,29,39
Later (1960-1973)	1,726	5	9	18,19,20,31
Urokinase Pulmonary Embolism Trial (1970)	78	9	19	32

I think not; there are several serious problems with the studies that probably explain the differences. Most likely many patients in earlier series did not have pulmonary embolism as UPET was the only series cited that required angiographic or lung scan documentation of the diagnosis. Patients with pulmonary embolism in the earlier series may also have been less critically ill than those in later series. Finally, follow-up may have been more extensive in the later series, leading to the detection of more deaths.

Only two prospective studies of this issue have been done. In 1960 Barritt and Jordan compared two weeks of anticoagulation with supportive therapy alone in the only randomized trial of anticoagulant therapy for pulmonary embolism.[17] They studied 35 patients with clinical findings of pulmonary infarction, acute right-sided heart failure, or both. Five of 19 untreated patients died of pulmonary embolism, in contrast to one death due to pneumonia among 16 treated patients ($P = .04$). Observing that "every patient who received the first injection of heparin survived," they urged the use of anticoagulation to reduce the incidence of early death from pulmonary embolism.

Serious questions about the validity of Barritt and Jordan's study may limit its applicability, however. The diagnostic criteria are inadequate by current standards, so we do not know how many of the surviving patients had pulmonary embolism. Furthermore, it is unclear whether treated and untreated patients were comparable in terms of severity of illness and duration of symptoms at the time of randomization. It is noteworthy that three of the five patients who died in the untreated group had fatal diseases other than pulmonary embolism. Finally, it is a small study in which only part of the spectrum of pulmonary embolism was examined and, therefore, their conclusions may not be generalizable.

A second study deserves mention not because of its methodologic rigor but because its astounding results highlight our therapeutic dilemma. Johnson and Charnley reported their experience with 628 patients with clinical diagnoses of pulmonary embolism following total hip replacement.[21] One of the 295 anticoagulated patients and none of 308 untreated patients died. Such results can be explained only by the inaccuracy of clinical diagnosis or by a wide spectrum of diseases due to pulmonary embolism.

On the basis of the above review I must conclude that the effects of heparin and coumarin derivatives on the morbidity and mortality of acute pulmonary embolism are not known. To the best of my knowledge, no data regarding the proper intensity or duration of therapy for pulmonary embolism alter this conclusion.

Do we know any more about other antithrombotic agents, specifically thrombolytics? We do, although our knowledge is only in reference to heparin, a therapeutic standard of dubious value.

The effects of both streptokinase and urokinase on pulmonary embolism have been studied extensively, especially by UPET. UPET randomly selected 160 patients with angiographically recorded pulmonary embolism for 12 hours of intravenous administration of heparin or urokinase followed by long-term anticoagulation. Angiography and hemodynamic studies were repeated at 24 hours, morbidity and mortality rate were assessed at two weeks and perfusion lung scans were done serially over the subsequent year. There was no significant difference in mortality rate (9% versus 7%) or recurrent embolism (19% versus 15%) in the heparin and urokinase groups, respectively. Compared with heparin, urokinase and streptokinase led to small but significant improvements in hemodynamic, angiographic and scan results at 24 hours and in pulmonary perfusion and diffusion at one year.[32,33] Also, patients with larger emboli generally showed the greatest angiographic and hemodynamic response to thrombolytics.[32,34,35] No clinical correlate of any of these laboratory differences has been detected, however.

How do we choose between heparin and thrombolytic therapy? Thrombolytics lead to slightly more rapid clot resolution and hemodynamic improvement, especially in patients with larger emboli, and to long-term improvement in pulmonary diffusion and perfusion. Thrombolytics, however, increase the risk of bleeding, lead to rare allergic reactions and cost more. Thus, although thrombolytics and heparin are reasonable therapies for pulmonary embolism, neither is clearly superior nor even of proved clinical benefit.

This conclusion is of concern for two reasons: First, unproved treatment that can lead to life-threatening complications is not benign. Second, the lack of a clearly beneficial therapy mandates a search for such therapy.

Are the risks of antithrombotic therapy so great, though, that we should not use it for its possible if unproved benefit? Again, the final answer is not in, but some relevant points should be considered: In four large randomized trials heparin and streptokinase for the treatment of different thromboembolic diseases were compared in 941 patients.[32,36-38] Serious bleeding and death due to bleeding developed in 3.5% and 0.5%, respectively, of the 467 patients treated with heparin and in 7.5% and 1.0%, respectively, of the 484 treated with streptokinase. In studies of anticoagulation agents given orally, bleeding complications developed in from 0% to 20% of patients in three months of therapy.[39] Although the risk of hemorrhage can probably be lessened by giving heparin continuously rather than intermittently and by maintaining the prothrombin time less than 2.5 times control or even in lower ranges,[39,40] it is clear that any antithrombotic therapy can lead to serious complications.

New Therapies

Two areas of current investigation may improve the medical treatment of acute pulmonary embolism. As we have seen, platelet secretions such as thromboxane probably cause many of the acute cardiopulmonary effects of pulmonary embolism. The experimental evidence reviewed earlier suggests that inhibition of throm-

boxane synthesis or prostacyclin infusion may alter the immediate course of pulmonary embolism.[10,41] This finding deserves further investigation.

Although we may attempt to benefit our patients by altering the humoral consequences of pulmonary embolism, it is clear that the embolus itself remains the prime instigator of both mechanical and humoral effects. A lytic agent that would limit its action largely to the embolus might be safer and more effective than current therapy. Two such agents have been developed,[42,43] the more promising being tissue-type plasminogen activator, or TPA.

TPA is an intriguing protein. Its discovery was supposedly related to the observation that the blood of corpses often clots for only an hour or so after death before it becomes fluid again. Hemoperfusion of such corpses led to the isolation of a so-called tissue-type plasminogen activator that was released from the endothelium in large quantities after death and that is different from the kidney-type plasminogen activator, urokinase.

TPA is a key factor in the process of physiologic fibrinolysis that keeps us all from turning into clot.[44] A 527-amino acid serine protease, single-chain TPA, is activated by proteolytic cleavage which may occur on binding of TPA to the fibrin in thrombus. TPA then activates plasminogen in the thrombus so thrombolysis occurs without development of a systemic lytic state. Streptokinase and urokinase, in contrast, lyse thrombus by activating enough plasminogen in the serum to overcome inhibition by antiplasmin, thus leading to a systemic lytic state as well as thrombolysis.

The important difference between tissue-type plasminogen activator and other thrombolytics is that TPA is clot-specific. Because it is active only when bound to fibrin, it does not cause the systemic lytic state caused by urokinase and streptokinase. In femoral vein thrombolysis in dogs, for example, urokinase led to fibrinogen depletion and the generation of fibrin-split products whereas TPA did not.[45] Bleeding complications have not been reported in animals given TPA, presumably because of the absence of the lytic state.

The major limitation to the use of TPA has been supply; corpse hemoperfusion is, at best, a cumbersome technique. Workers at Genentech have recently cloned the gene for TPA from human melanoma cells and have produced therapeutic quantities.[46] Despite concerns that a synthetic polypeptide as complex as TPA might not function, recombinant TPA administered by vein has recently been shown to lyse coronary thrombosis in cats (David Martin, MD, oral communication, May 1983). Whether TPA will have such dramatic effects in lysing pulmonary emboli remains to be seen.

Conclusion

Streptokinase and urokinase, in comparison with heparin alone, improve short-term angiographic and hemodynamic results and long-term pulmonary diffusion and capacity. Neither anticoagulants nor thrombolytics, however, have been proved to alter the morbidity or mortality of acute pulmonary embolism or to have long-term clinical benefit. The risk of bleeding is not well defined, but antithrombotic therapy may cause death in as many as 1% of patients and serious bleeding in about 5%.

Present experimental and clinical data, therefore, do not justify a therapeutic dogma. While traditional antithrombotic therapy such as that studied in UPET is perhaps the most reasonable present treatment of pulmonary embolism, it remains unproved and should not encourage our complacence. Future clinical trials might investigate issues such as the use of TPA compared with heparin and perhaps placebo, the effects of altering prostaglandin metabolism and the roles of surgical intervention and long-term anticoagulation. Until such trials have been done we will not know the best therapy for pulmonary embolism.

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Epitomes

Important Advances in Clinical Medicine

Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in plastic surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Breast Reconstruction

RECONSTRUCTION of the breast following mastectomy is becoming more common as women become more aware of surgical alternatives and as newer techniques develop. Even women with significant chest wall deformities due to radical mastectomy and radiation therapy are candidates for breast reconstruction unless other systemic disease precludes an elective surgical procedure. The type of reconstruction is contingent on the degree of chest wall deformity. Each operation must be designed for the individual patient and with the objective of obtaining symmetry.

For suitable candidates, some centers are now enthusiastic about immediate breast reconstruction using an expandable submuscular prosthesis placed at the time of mastectomy and slowly inflated. Later, after appropriate skin expansion, the prosthesis is removed and replaced with a permanent implant followed by nipple-areola reconstruction. In selected cases the implant may be placed without the use of an expander.

When the pectoralis muscles have been removed and the overlying skin is tight and scarred, additional skin and muscle are needed to create the most symmetric reconstruction. The latissimus dorsi musculocutaneous flap is an excellent choice in this situation and can produce predictably reliable results when placed over a gel-filled implant. There is considerable enthusiasm regarding a lower transverse abdominal flap based on the rectus abdominis muscle, which allows for successful breast reconstruction using autogenous tissue and avoids the need for an implant. The donor site incision usually closes similarly to that of an abdominoplasty and results in a tighter and trimmer abdominal wall and a soft and symmetric reconstructed breast.

After an adequate breast mound has been created, one can reconstruct the nipple-areola complex using a variety of tissues. In the usual reconstructive procedure the pigmented skin on the medial aspect of the thigh is used for the areola, and a shared portion of the opposite nipple or earlobe is used to reconstruct the nipple.

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Limb Salvage

LIMB SALVAGE, now a well-recognized technical feat, must be measured against the useful function restored and that which can be provided by a prosthesis. In the upper extremity restoration of sensate key pinch, chuck pinch and tubular grasp are the primary objectives, in that order. In the lower extremity restoration of functional gait with a sensate foot is the sole objective. Lower extremity length is of prime importance, but a useful upper extremity may be many centimeters shorter than a normal one. High amputations should only be replanted under the most ideal conditions in the arm and almost never in the lower extremity. Protective sensation on the sole of the foot and useful sensation on the hand will take up to two years or more to develop. It may never occur if there has been a traction injury to the proximal nerves, plexes or nerve roots.

Neurotrophic ulcers or injuries to the replanted part are a constant problem during this recovery phase.

The massive amount of muscle tissue present in high amputations is extremely vulnerable to ischemia and replantation of the part may result in life-threatening complications when the circulation is reestablished. Time is of the essence in all major limb replants. Immediate arterial and venous shunts should be inserted to shorten this critical period of ischemia before bone stabilization or any soft-tissue repair.

The most common extremity salvage situation exists when there has been a severe compound comminuted lower extremity fracture with extensive soft-tissue injury. Exposed bones, joints and tendons with or without metal plates and rods must be covered by vascularized tissue. The use of proximally and distally based muscle and myocutaneous flaps often leads to further tissue loss in an already severely traumatized extremity. Wound cover can best be achieved by microvascular transplantation of muscle, with the vascular supply anastomosed to untraumatized proximal vessels. These pliable muscle structures can be wrapped around and folded into defects, obliterating dead space and bringing in needed blood supply. Ideally these transplants should be done as primary or delayed primary operations. If reconstruction is delayed for several weeks, severe problems with acute and chronic osteomyelitis are encountered. When wound closure and control of infection have been achieved, then secondary vascularized bone grafts and other procedures can be undertaken. None of these operations are indicated if the nerve supply to the sole of the foot has been destroyed.

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Kutz JE, Hanel D, Scheker L, et al: Upper extremity replantation. Orthop Clin North Am 1983 Oct; 14:873-891

Craniofacial Surgery

While the comprehensive care of rare and highly complex congenital craniofacial anomalies has been left to a few centers, the application of craniofacial surgical principles and techniques has become widespread.

The classic use of autogenous iliac and costal bone grafts to repair the facial skeleton has been largely replaced by the use of cranial bone grafts. The outer table and the diploë can be safely harvested as a split graft. Aside from its use in craniofacial surgical procedures, it has been applied to correct saddle-nose deformities, erase alveolar clefts in children with cleft palate, repair orbital floor fractures and restore the contour of cranial defects. Resorption of the graft is minimal. Donor site pain and morbidity, when compared with that of the ilium and rib cage, are greatly reduced, as is the hospital stay.

In cases of severe maxillofacial trauma, the availability of computed tomographic scanning, immediate bone grafting and direct exposure and fixation of the fractures have improved the end results and lessened the need for secondary reconstruction. Difficult late residual problems such as enophthalmos can also be corrected by using craniofacial surgical approaches and techniques.

Parts of the facial skeleton are frequently electively moved to improve form and function. In conjunction with an orthodontist, difficult skeletal bite deformities can be corrected by simple procedures. Both jaws can safely be simultaneously repositioned to bring about dramatic changes.

Working as a team, plastic surgeons and neurosurgeons have augmented the time-honored stripping of craniosynostosis by repositioning the deformed bones in early infancy. The deleterious late deformity is thus lessened. In an older age group, treatment of a disfiguring craniofacial malformation has been simplified and the operating time drastically reduced, hence decreasing the morbidity and mortality of the procedure.

Thus, while the refinement in craniofacial procedures continues in selected centers, the spin-off of techniques enjoys wide application to the entire specialty of plastic surgery.

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Recent Advances in Ear Reconstruction

Reconstruction of the ear for microtia, traumatic loss or burn sequelae has, until recently, rarely resembled the natural color and contour of a normal ear. After undergoing numerous procedures, patients were often left with noticeably deformed, scar-encased auricular facsimiles. Silicone frameworks have been disappointing as they have an unacceptably high incidence of eventual exposure, infection and extrusion.

In virgin microtia, skin coverage is usually not a problem. Brent has shown that precision sculpting of autogenous rib cartilage with exaggeration of natural prominences produces excellent contours. Proper projection can be obtained by a supportive postauricular cartilage block. A deep posterior sulcus is not reconstructed.

For posttraumatic losses or extensively scarred, failed previous surgical procedures, the temporoparietal fascia used as a vascularized flap affords the greatest opportunity for an aesthetic reconstruction. The old scar is totally resected and the carved rib cartilage is inset. The temporoparietal fascia is then

raised as a pedicle flap and draped over the cartilage framework. This is covered with a thick split-thickness skin graft. Because of its filmy and highly vascularized nature, the temporoparietal fascia both conforms beautifully to the cartilaginous foundation and serves as a reliable vascularized bed for both the cartilage and the overlying skin graft.

Brent has reported an extensive experience with this procedure and notes the operation to be extremely dependable with minimal complications. Other centers have had similar favorable results.

Repair of congenital contour ear deformities without tissue shortage in midchildhood or later is a difficult surgical procedure with mixed results. Recent reports by Matsuo and co-workers from Japan have shown the efficacy of correcting auricular deformities in the neonate by nonsurgical methods. Prominent ears, cup and lop ears and other abnormal shapes are corrected by combining molding and tape splints. This must be initiated immediately postpartum and held for about four weeks for the cartilage to be permanently reshaped. The procedure requires skilled application and careful monitoring to be effective and still avoid complications such as tissue necrosis.

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Suction-Assisted Lipectomy, Suction Lipectomy, Lipolysis and Lipexeresis

THE TERMS suction lipectomy, lipolysis and lipexeresis are applied to a surgical procedure commonly known as "fat suctioning." Over the past two or three years the lay press has extolled its virtues for the treatment of "cellulite."

Historically, this technique is an offshoot of a curettement technique through a small incision. First made popular by Schrudde of Cologne, West Germany, in the early 1960s, this technique consisted of using a small incision and curetting out, through a tunnel made with a long pair of scissors, the fat of primarily the hips, knees, thighs and ankles. Dr Schrudde currently uses a suction cannula.

The surgeon who deserves the credit for developing the suction cannula is Ulrich Kesselring of Lausanne, Switzerland. Beginning in the 1970s Dr Kesselring used a relatively large cannula with a large aperture for carving the fat. His results have been excellent with minimal complications.

In 1977 Yves-Gerard Illouz of Paris began using a smaller type suction cannula with a high vacuum suction of about 743 mm of mercury. With this technique, large areas have been done with minimal complications such as seroma, hematoma and skin loss.

The technique is designed primarily for localized deformities such as the "riding britches syndrome," the "saddlebag deformity," bulging of the medial aspect of the knees and bulging of the abdomen, around the waistline in the flank and in the axilla and the chin. These areas have all responded well to the suction technique, the only scar being the puncture site, usually in one of the normal skin folds. The results in patients with good skin turgor and good fat density have been exceedingly gratifying.

Surprisingly, this procedure lends itself well to refinements and enhancement of normal aesthetic body contouring procedures such as abdominoplasty and thigh reduction by allowing a surgeon to minimize the extent of the dissection and length of the incision. In an abdominoplasty, deepening of the midline raphe by suction-assisted lipectomy gives a patient a more youthful appearance to the abdomen. The usual dog-ears in the traditional operation can often be eliminated without extending the incisions well over into the hip and flank area. We have also found it very useful in a facelift where suctioning the fatty tissue of the neck is accomplished and in breast reduction where there is fullness of the axilla.

Suction-assisted lipectomy has been of further benefit in many of the reconstructive operations using free flaps or transposed flaps that have irregular contour fitting. There symmetry can be improved after the wounds have healed. It has also been useful in aspirating some areas that have been injected with liquid silicone. In addition, a number of lipomas have been removed successfully using a suction cannula.

Future research with this technique may offer some help to obese and diabetic patients. Currently suction-assisted lipectomy is a useful technique in repairing local deformities and in conjunction with traditional body-contouring operations to enhance their results.

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Noninvasive Monitoring of Tissue Viability

SIMPLE AND accurate methods for predicting tissue survival will be increasingly important as reconstructive procedures reach new horizons. Work in our laboratory and others has been improving noninvasive monitoring methods.

One notable method is the use of a surface fluorometer (Fluoroscan). Blue light is transmitted to the skin surface through a flexible fiberoptic pathway. Fluorescein molecules present in the skin emit yellow-green fluorescence that is carried back through the same fiberoptic pathway and converted to a digital readout. Graham and co-workers have shown that this instru-

ment is 500 times more sensitive than the human eye using a Wood's lamp. They have also shown that the Fluoroscan is able to predict skin-flap survival in rats. In clinical and experimental studies, we have found it simple and reliable, using less than a tenth the dose of fluorescein we had formerly used for visual assessment with a Wood's lamp. Testing may be easily repeated at frequent intervals.

Another method is transcutaneous oxygen partial pressure (Po_2) monitoring. Monitoring devices measure alterations of current in a polarographic cell induced by changes in Po_2. Most units contain a simple heating element to produce vasodilatation in the area being monitored. Thermal burns are therefore possible with prolonged monitoring at higher temperatures. Instruments that function at lower temperatures should eliminate this danger. Smith and associates have reported their experience with 65 replantations and 18 free tissue transfers. In failing replantations or free tissue transfers, changes in Po_2 appeared several hours earlier than clinical changes or temperature changes. Our own experience has been similar.

With the increasing complexity of major reconstructive surgical procedures, we feel that these and additional noninvasive tissue monitoring techniques will have increasing clinical importance and applicability.

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Applications of Free Flaps

MICROSURGICAL ANASTOMOSIS of small vessels has become an indispensable method of transferring living tissue for reconstruction. Continuing investigation of the circulatory anatomy of skin, muscle, fascia and bone is expanding the repertoire of donor sites and treatable problems. The overall success rate of transfers of free vascularized tissue exceeds 95% when performed by experienced teams. Microsurgical training is now a part of most plastic surgery residencies, and additional training is available through active fellowship programs.

There are two areas of free flap applications: wound closure and reconstruction. Wound closure applications were discussed in the plastic surgery "Epitome" series in the June 1982 issue. As an update, free flaps are being most regularly used in closing defects due to a surgical procedure, trauma, irradiation or infection where local flaps are unsuitable, unavailable or will not heal. Heretofore-untreatable wounds can now be reliably closed in one stage. For problem wounds of the foot and the distal third of the leg, where muscle mass is sparse and cutaneous circulation is poor, closure with free flaps is now considered the treatment of choice.

Free flaps have permitted ever-increasing possibilities for reconstructive procedures. These applications include the following:

Skin. Thin flaps of skin alone can be transferred on direct cutaneous arteries to restore stability to large unstable scars. Some skin flaps (mostly from the back and extremities) have an identifiable sensory nerve that can be used to restore sensibility and are useful for reconstructing palmar and plantar defects.

Soft tissue. Serious soft tissue defects of the face due to injury, irradiation, hemifacial atrophy and craniofacial anomalies can be corrected. Flaps of muscle, omentum and de-epithelialized skin are used. For women who do not tolerate prostheses, free flaps of abdominal or buttock skin and fat have been used for breast reconstruction.

Muscle. Palsies of the face and hands, of many causes, can be reanimated by vascularized muscle transfers with motor neurorrhaphy. The gracilis and foot muscles have been the most useful.

Skeleton. Management of large skeletal defects has been improved by the realization that bone healing is superior with vascularized rather than conventional grafts. Vascularized grafts of rib, ilium, fibula, scapula and metatarsal are often the preferred treatment for many defects of the mandible, femur, tibia and upper extremity.

Viscera. Defects of viscera, such as pharynx, trachea and ureter, have been reconstructed experimentally and clinically with transfers of soft tissues or other viscera such as jejunum or appendix. Many of these have been singular cases, but the value of pharyngoesophageal reconstruction with jejunum or colon has been established.

The most important recent development is the custom design of free flaps. Isolated vessels can be transposed underneath an otherwise random flap. As healing occurs, vascular continuity is established between flap and pedicle and the entire unit can then be transferred. This has been successful experimentally and clinically.

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Use of Nasendoscopy in the Treatment of Velopharyngeal Insufficiency

PERSISTENT VELOPHARYNGEAL INSUFFICIENCY is variously described as occurring in up to 20% of any series following closure of a hard- or soft-palate cleft. Since 1876 the treatment of choice—though recently challenged by pharyngoplasty—has been creation of a pharyngeal flap. Though overall success following a

pharyngeal flap operation has been relatively high, there unfortunately remains a hard core of unsuccessful cases, the reasons for which were unclear until recently. While a number of theories existed as to why the creation of a pharyngeal flap was successful, it has only recently become clear that the sole function of the flap is as an obturator. As a result, it was postulated by several workers in 1972 that the success or failure of the pharyngeal flap was directly related to the adequacy of lateral pharyngeal wall motion. Numerous studies have since confirmed this postulate and it has been clearly shown that postoperative results following a pharyngeal flap operation are based entirely on the adequacy, or lack thereof, of lateral pharyngeal wall movement.

Shprintzen in 1979, Argamaso in 1980 and Daniller and colleagues have shown that the use of preoperative planning allows for the creation of pharyngeal flaps tailormade to the size, shape and location of the velopharyngeal gap. Using a combination of videofluoroscopy and fiberoptic nasendoscopy, it is possible to tailor a wide flap where there is minimal or no lateral pharyngeal wall movement, a narrow flap for situations where there is extremely good lateral pharyngeal wall movement as commonly seen with submucous clefts.

While a combination of multiview videofluoroscopy and nasopharyngoscopy is the best way of obtaining accurate preoperative information, in an average practice it is logistically easier to obtain accurate nasendoscopy information than it is to obtain a combination of the two techniques. Use of a flexible fiberoptic nasopharyngoscope has greatly increased the ability to make accurate preoperative diagnostic judgments on the function of the velopharyngeal port and it can be done easily in an office setting.

Whereas no one flap has been found to be superior to another, it has been possible to tailor the size of flaps by reducing the amount of postoperative tubing. A flap that undergoes very little tubing will remain broad; one that is allowed to tube will basically become fairly narrow. Lack of tubing can be predicted when the superiorly based pharyngeal flap is of the sandwich variety. A superiorly based musculomucosal flap is raised in a routine manner and then sandwiched into a pocket created in the soft palate that extends from one tonsillar pillar to the other. The tubing effects on the broad, relatively short, unattached segment have been less pronounced than those observed with other varieties of superiorly based pharyngeal flaps. With the use of a 3-mm fiberoptic nasendoscope and topical anesthetic, it is possible to examine even very young children and obtain very high success rates. Thus, using careful preoperative nasendoscopy planning, it is possible to successfully treat patients with velopharyngeal incompetence, reducing persistent postoperative velopharyngeal incompetence to a minimal level. A secondary pharyngeal flap surgical procedure, while not impossible, can be extremely difficult. Reducing the chances of failure by using careful preoperative diagnostic planning has dramatically reduced the necessity for a second operation.

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Collagen

SINCE 1977 when Knapp and others reported their preliminary work on the use of injectable collagen, a large number of patients have been treated in an attempt to correct a variety of textural and contour problems with various degrees of success and permanence of results.

The collagen implant, supplied as a dispersion in preloaded sterile syringes, is injected into the superficial dermis through a 27- or 30-gauge needle using a multiple-puncture technique. The material is suspended in saline and 0.3% lidocaine and is provided in two concentrations of 35 and 65 mg per ml. Studies in animals and human tissue biopsy specimens indicate that the collagen mass condenses into a cohesive implant that serves as a matrix for the ingrowth of fibroblasts and capillaries.

Before treatment, an intradermal skin test is administered on the forearm and the site is observed for four weeks to determine if any sensitivity develops. A positive skin test has been observed in 3% of recipients; they, of course, are not treated. Patients with a history of autoimmune disease or a strong allergic history should not be treated. After a negative skin test, injections are given at two- to four-week intervals, overcorrecting to 150% to 200% each time. Usually three to four sessions are required.

It is important that the texture, contour and induration of the lesion to be treated be carefully considered. Small cutaneous depressions, scars from acne, surgical procedures and trauma, depressed skin grafts and some of the changes, wrinkles and depressions due to the aging process have been treated successfully. Sharply marginated lesions such as chickenpox scars or the "icepick" scars of acne are difficult if not impossible to treat. Steroid atrophy, linear scleroderma, hemifacial atrophy and some of the residual contour abnormalities associated with cleft lip have been treated experimentally. Scars that are soft, distensible and nonstressed respond well, whereas those that are excessively firm, indurated or nondistensible do not. Occasionally, very firm areas will soften under treatment.

Problems and complications such as local tissue reaction, infection or laceration of a superficial tiny blood vessel occur in less than 1% of patients. The development of sensitivity or an allergic response during the course of treatment is also less than 1%. Significant, severe or systemic complications are rare. A single case

of occlusion of an intraocular vessel has occurred with a periorbital injection.

The long-term results of collagen injections to correct contour deformity vary with the type of lesion, tissue stress and unknown factors related to collagen turnover. Patients are advised that the permanence of the correction cannot be predicted and that some subsidence will occur. Supplemental injections may be required to maintain adequacy of results; however, good results without reinjection have occurred in a significant number of patients for as long as two to four years.

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Refinements in Tissue Expansion

TISSUE EXPANSION represents a physiologic phenomenon that emphasizes the principle that tissue can accommodate to a slowly enlarging mass by increasing its surface area. Developmental expansion of breast tissue or the cyclical enlargement of abdominal girth by a growing fetus are pertinent examples of natural tissue expansion.

"Controlled" tissue expansion was popularized by the innovative developments, begun by Dr Chedomir Radovan in 1976, for adjacent flaps in breast reconstruction. Since then, the use of tissue expansion in reconstructive surgery has sharply widened in both clinical and research areas.

Tissue expansion is a two-staged technique initiated by placing a temporary expandable silicone implant beneath normal tissue, usually adjacent but, on occasion, distant to a defect. As the silastic balloon is enlarged by the incremental addition of sterile saline, the overlying tissue gently "expands" and is available for use after implant removal. Tissue expansion should be considered an *aesthetic* alternative in reconstructive surgical procedures, specifically in those areas where previous techniques have not provided consistent aesthetic or functional results. Because of its versatility, safety and simplicity, tissue expansion may be better tolerated in patients where more sophisticated and complicated procedures may prove to be a substantial challenge to the patient's problem.

Advantages

- Minimal donor defect.
- Provides "like" characteristics, such as color, sensation, hair.
- Provides highly vascularized tissue—that is, delay phenomenon.
- Simple, reliable, safe and versatile.

Clinical Usage

- Head and neck reconstruction—that is, scalp, nose, external ear, mandible, congenital nevi and hemangiomas, traumatic and cosmetic defects and burn contractures.
- Breast reconstruction for Poland's syndrome, postmastectomy.
- Trunk and perineal reconstruction for burn contracture, abdominal wall defects, pressure sores and the like.
- Extremity reconstruction for pressure sores, traumatic defects and so forth.

Preventing complications remains the key to reducing the rates of major and minor complications. These include proper patient and defect selection, refining operative techniques and improved product modification. The common complications of tissue expansion include exposure or deflation of implant and valve, infection, skin necrosis, compression of adjacent structures and hematoma or seroma.

With any innovative reconstructive procedure, a period of enthusiasm is followed by a period of reflection and refinements. The concept and practice of tissue expansion is currently in the latter period of evolution. Its ultimate role in reconstruction will be determined by increased clinical experience and the ingenuity of surgeons.

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Biobrane—A Synthetic Skin Substitute

THE DEVELOPMENT of an artificial skin to replace burn-damaged skin has been a long-held hope. Recent publications in the lay press have brought this research to the attention of the general public and have raised its expectations.

A truly artificial skin would ideally be a *permanent* substitute for a patient's own skin and, as such, should share with skin the characteristics of a protective barrier against bacterial invasion and water, protein and heat loss. The ideal artificial skin would also be flexible, sterile with a long shelf life, low in cost and readily available. In the recent past and at present, the best skin substitutes have been biologic dressings such as amnion and human cadaver allograft. These are expensive, however, must be changed frequently and are not permanent, requiring eventual replacement with autograft.

A commercially available synthetic skin substitute, Biobrane, has been widely used on burned patients as a temporary skin replacement. It has served as a low-cost alternative to human cadaver allograft. The barrier properties of Biobrane are similar to human skin; it is able to withstand bacterial wound contamination as well as fresh human cadaver allograft and is transparent, allowing visualization of the underlying wound.

While still requiring eventual replacement with autograft, Biobrane serves to protect the excised burn wound from internal fluid loss and external contamination and can remain in place for many weeks. To have a knitted nylon-silicone rubber membrane coated with collagen peptides replace most of the functions of normal skin, albeit temporarily, is a definite advance over other currently available dressings.

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Burn Wound Coverage

THE THERAPEUTIC IMPERATIVE in the care of patients with extensive burns is wound closure. Failure to promptly restore the impaired skin barrier leads to continuing fluid and electrolyte disturbances, malnutrition and bacterial invasion. The ideal burn wound cover is, of course, autogenous skin. In extensive burns, there is a limited supply. Closure of these wounds with temporary skin substitutes allows time for reepithelialization and reharvesting of donor sites.

In the search for a substitute, several biologic and synthetic wound coverings have been used. The ideal substitute is one that adheres to the wound, allows water vapor transport, minimizes protein and heat loss, has elastic properties, is durable and flexible, maintains an intact bacterial barrier, is nonantigenic and nontoxic, antiseptic and hemostatic, is applied and removed easily, has a long shelf life and, finally, is readily available and affordable. The current available skin substitutes, none of which is ideal, include

- allografts—living donor; cadaver fresh, frozen; amnion.
- xenografts—fresh, frozen, irradiated or dried.
- tissue derivatives—collagen sheet, fabric or sponge and Bioplast fibrin.
- synthetic material—solid silicone polymer membrane, other plastics, microporous materials, adherent materials (Hydron).
- composite material—surface membrane (silicone, micropores); adherent substrate (collagen, cotton gauze, synthetic, polymer, sponge, velour, flocking or fabric).

Allografts are the closest to the ideal temporary wound cover. The limiting factors include expense, frequent changes, nonpermanence, antigenicity and availability. Recent advances in immunomanipulation, however, allow one to use allograft for prolonged periods, systematically replacing it with autogenous skin grafts. Amnion is limited by availability, pigskin by its imperfect adherence and inability to control bacterial growth and the synthetics by their poor adherence and inability to control bacterial growth. A "skin equivalent" has been developed by tissue culture techniques that, although promising, is limited by the time needed to "grow" the skin. The most promising substitute is the composite artificial skin developed by Burke and co-workers. This "skin" is a bi-layer of artificial skin composed of a temporary Silastic epidermis and a porous collagen-chondroitin six-sulfate fibrillar dermis. Following grafting, the "neodermis" serves as a template for synthesis of new connective tissue. When donor sites are ready for reharvesting, the Silastic epidermis is removed from the vascularized dermis and replaced with 0.004-in autoepidermal grafts.

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Editorials

The Practice of Medicine Is Changing—or Is It?

THESE ARE TIMES for physicians to reflect upon why we came into medicine in the first place and perhaps to consciously rededicate ourselves to the ideas and ideals that inspired us in our earlier years when, for most of us, things were very different. While the money they thought they might earn may have motivated some, there must have been easier ways for them to get it. Most of those who were merely after money were smart enough to have made as much or more of it in other ways with a lot less demand on their talent and time. Money has always been important, of course, but physicians generally have been able to live comfortably and to practice conscientiously without thinking very much about money. But all this has changed. There is now good reason to believe that money will soon affect almost every decision in medical practice and almost every aspect of patient care, and this through no fault of practicing physicians or their patients.

The heart of medical practice is a physician, a patient and what takes place when the one seeks help and the other tries to help, using knowledge, skills, care and understanding that have been learned through training and experience. The patients who seek help have not changed very much, and the young men and women entering medical schools today have very much the same desire to help their fellowman and the same fascination with unfolding biomedical science that motivated most of us to join this profession in years past. The heart of medical practice has not changed, and the heart in it is still there, still warmly rewarding physicians who are able to relieve suffering, anxiety or pain in the patients who seek their help. These are times of almost unprecedented stress for physicians trying to practice good medicine, but each of us can gain the inner strength that is needed by making a conscious rededication to the ideas and ideals that brought us to this noble profession in the first place. Perhaps more of us should do this at this troubled time. We can also take genuine comfort in the reality that the more the practice of medicine changes, the more it remains the same.

MSMW

Reye's Syndrome—Still an Elusive Entity

REYE'S SYNDROME, first clearly described in 1963,[1] continues to be an elusive entity in 1984. Ideas concerning its etiology have come almost full circle from Mortimer and Lepow's early report of "varicella with hypoglycemia possibly due to salicylates"[2] to the recent epidemiologic evidence linking Reye's syndrome with salicylate use. Is the disorder merely a form of aspirin poisoning? The answer probably is not as simple as that. More likely, genetically determined susceptibility plus a complex interaction between toxicity of certain viruses and salicylate effects lead to the damage to mitochondria that underlies Reye's syndrome. A transient decrease in activity of multiple mitochondrial enzymes in turn explains all of the major clinical and laboratory findings including hyperammonemia (due to inhibition of the two mitochondrial enzymes of the Krebs urea cycle), fatty acidemia (due to interference with mitochondrial fatty acid oxidation), lactic acidemia (due to decreased activity of pyruvate carboxylase), accumulation of biogenic amines and aminoacidemia. Serum levels of several metabolites, including ammonia and lactate, correlate well with the severity of the central nervous system dysfunction.[3,4] The central nervous system toxicity of some, such as ammonia and short-chain fatty acids, is now well understood. Even the cerebral edema that frequently complicates Reye's syndrome can be explained on the basis of mitochondrial damage. To a large extent, it appears to be myelin edema, the same type seen experimentally in response to mitochondrial poisons such as triethyltin.[5]

The treatment of Reye's syndrome continues to be a controversial subject. The "therapeutic delirium" pointed out by Nadler in 1974[6] persists today. Many patients recover spontaneously without any therapy other than the intravenous administration of hydration and glucose. Almost everyone agrees that treatment of children who are awake should be limited to such simple measures. The approach to a comatose child varies greatly. Invasive measures including the placement of intracranial pressure monitors, administration of curare and artificial ventilation, hypothermia, barbiturate coma and exchange blood transfusion are used in various combinations and for various indications. Many experts apply such measures to all comatose children who have Reye's syndrome. Yet it is likely that many of these children would recover with less invasive approaches. Patients in whom metabolic variables such as blood ammonia and lactate levels are only mildly elevated early in the course appear to do well no matter what treatment is used,[3,4] provided that they are not injured by the therapeutic attempts. The tragedy of survival with severe, persistent brain damage, rare during the early days of treating Reye's syndrome, is now a relatively common occurrence with up to 20% of patients falling into this category in some series.[7] Injudicious use of hyperosmolar agents for control of cerebral edema is another possible cause of injury. Hyperosmolar coma, cerebral hemorrhage and disturbances of blood-brain barrier functions may result from such agents. Yet, they may be lifesaving in

some patients. Better criteria for selecting those patients who may benefit from invasive measures are urgently needed, as is critical appraisal of the effects of each measure used. Barbiturate coma, initially introduced as a major advance, may on balance do more harm than good.[7] Even intracranial pressure monitoring, used almost universally in severe cases, has not been shown to lead to improved outcome.

The best cure naturally is prevention. Exciting developments are taking place in this area. Trauner summarizes the evidence linking Reye's syndrome to salicylate use. In the midwestern states an intensive publicity campaign warning against salicylate use for treatment of fever in childhood was started almost three years ago. There is every indication that this has notably influenced the pattern of antipyretic drug use in children. The initial results of this change look encouraging. The incidence of Reye's syndrome in the Midwest has decreased greatly in the past two to three years. In our own institution we have seen only two cases in the past two years, where we would have expected to see 10 to 20. Both had been given salicylates, one for treatment of chronic arthralgia, the other because the mother was unaware that the home remedy she administered to the child contained salicylate as a major ingredient.

Other factors, such as a change in the pattern of viral disease, may explain the recent decrease in the incidence of Reye's syndrome. This large uncontrolled and uncontrollable population study is continuing, with monitoring of case incidence by the state health departments and by the Centers for Disease Control in Atlanta. Every year that Reye's syndrome remains rare where antipyretic use of salicylates is low will increase the likelihood of a cause-effect relationship. At best, there probably will always be some cases of Reye's syndrome, both in children who require salicylates for treatment of chronic illnesses such as juvenile rheumatoid arthritis and, occasionally, in children with high susceptibility in whom exposure to virus alone without the added factor of drug toxicity may precipitate this reaction. In addition, newly introduced drugs may produce new outbreaks of similar syndromes, as is suggested by recent experience with valproic acid.[8]

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On Measuring Both Quality and Costs in Patient Care

THE OBVIOUSLY growing concern with costs in health care and the present emphasis on encouraging competition in this field are already having profound effects. Some may prove to be detrimental while others may bring about improvement. There is also concern that measures to reduce costs may impair the quality of the care rendered. But adequate objective measures of quality in health care have been difficult to come by. All of this has been widely recognized and discussed in both the public and private sectors. So far it has been loudly proclaimed that quality must not be sacrificed but that somehow costs must be contained. The responsibility to accomplish this has been placed on the integrity of the patient's physician to do what is necessary at the least cost and then reliance on peer review of hospital care and of patient care charges to see that this is done. The need for better and more objective approaches to assuring and even improving quality in patient care while responding reasonably to cost considerations is clear enough.

The challenges of the new competition and the imperative to reduce costs combine to require more reliance on objective data in health care. Computers have enormously facilitated this process. For some time now third party insurers, both private and governmental, have had sophisticated computerized data on how, where and by whom health care is rendered. More recently data bases on patient care have developed within many kinds of health care delivery systems including HMOs, IPAs, PPOs and no doubt now in some of the more recent contracting arrangements. The advent of DRGs (so far only for Medicare patients) is now causing hospitals, both for-profit and nonprofit, to hasten to develop objective patient care data to help them and their medical staffs get a better handle on their own health care costs. And one does not need a crystal ball to see that the need for an objective data base for any kind of practice arrangement may not be too far over the horizon. This increasing reliance on objective data bases in health care is one of the profound and far-reaching effects of the growing concern with costs and the present emphasis on competition in health care.

These computerized data bases have been created to measure costs. But could they be used or adapted to measure quality as well? There are some analogies that seem worth considering. Physicians can be quite comfortable with developing data, studying and comparing results, and the principle of peer review. For example, in clinical research data are collected, results are studied and compared, and the findings are subjected to peer review. In the clinical care model new methods and new discoveries are given peer review, data and outcomes are compared, and what is best is introduced into practice. We call this the scientific method. And the experience with accreditation is worth noting. True, here the focus has been more on quality than on costs.

Its method is one of peer review, examination and comparison of data. Its standards of quality are based upon performance data and comparisons between institutions. The accreditation model has proved that over time it can actually raise standards by providing institutions with incentives to move to higher levels of quality. And when one thinks about it, there would seem to be no particular reason why the accreditation model could not be applied to quality of care and cost containment as well. But the point to be made here is that the methods that are coming into being to use patient care data to contain costs may not be all that different from the methods that are needed to develop and use patient care data to measure, assure and even improve quality—and even outcomes—in patient care, while at the same time relating quality, and possibly even outcomes, to costs.

The essential ingredients to measure and assure both quality and costs in patient care seem to be at hand. These include the basic integrity of the vast majority of physicians, the objective data bases that are now developing in every facet of patient care, and the experience with and general acceptance of peer review as a tool to assure quality. Thus it would seem that objective measures for both quality and costs can come from comparisons of objective data to be found in patient care data bases.

Elsewhere in this issue Howard Lang discusses the use of comparisons between services, DRGs, physician performance and the like in terms of costs. All that remains is to use similar or comparable comparisons to assess quality, and then to begin to find ways to relate these assessments of quality to the benefit obtained from the cost. Much of what is needed to do this is already accepted or in place. It is to be hoped that measures such as these comparisons of objective data can be developed and then adopted into general use so as to help meet the challenge of assuring patient care of good quality at affordable cost in these difficult but stimulating times.

MSMW

Clinical Application of Biological Research

THE SPECIALTY CONFERENCE, "Recombinant DNA in Medicine," elsewhere in this issue, describes numerous past and recent accomplishments aided by "recombinant DNA" technology and projects their impact on medicine. Although the rubric of "recombinant DNA" could be criticized ("modern biology" might be more appropriate), the introduction of this technology does provide a chronological marker of sorts for an infusion of excitement and rebirth into the field of molecular biology. In reading this article several considerations should be kept in mind. One must realize that "recombinant DNA" technology (or "gene splicing" or "DNA cloning") represents a collection of methodologies that provides a very powerful research tool for many areas of biology and medicine. These methodologies range from microbial genetics and enzymology to the chemical synthesis of DNA and the determination of nucleotide sequences of DNA. To simplify, this technology provides the wherewithal to manipulate, identify and purify segments of DNA from any organism and produce them in substantial quantity for analysis and investigative purposes. In addition, these are the core methodologies for the modern biotechnologic industry, which focuses on the production of useful and commercially viable biological materials or by-products.

In the past ten years since the "recombinant DNA" or "gene splicing" technology was first developed, significant improvements have continually enhanced the efficiency and resolution of molecular biological research. As a result the numerous achievements documented herein include some truly revolutionary discoveries in biology made in the past few years. The discovery of introns in the genes of higher organisms, the documentation of in vivo somatic recombination events as the mechanism for generating antibody diversity, the elucidation of the molecular basis of genetic diseases and the uncovering of a library of oncogenes are but a few examples. One can certainly anticipate further elucidation and understanding of the biological significance of these and other findings. It is equally clear that several other areas of biological interest will be affected by research based on these methodologies. Of particular interest to the medical community will be the thrust into the molecular biological mechanisms of the immune system, and the mysteries of neurobiology and mammalian development.

Notwithstanding the remarkable discoveries made in the past decade, one could ask how many patients have directly benefited from this research. The number must be small. Human insulin is not widely marketed, and only a small number of patients have been treated in clinical trials with the handful of biologicals developed in the biotechnologic industry. Nevertheless, as evidenced in the Specialty Conference in this issue, enthusiasm is widespread in the expectation for significant medical contributions at the patient level. The reason for the delay in direct patient benefits can be illustrated by considering the differences between basic research and the development of a biological product based on the results of basic research. The significant advances in basic research made to date derive from experiments designed to answer questions about biological mechanisms, which in turn generate intellectual constructs. In providing diagnostics or biological materials for the treatment of diseases or genetic disorders, one must first rely on the intellectual constructs as the basis for developing a useful product. The biotechnologists design and engineer an organism that synthesizes the product, and then large-scale production and purification systems must be developed. These processes must be carefully monitored to provide a quality-controlled product. Preclinical data must be gathered to obtain permission to conduct clinical trials. Clinical trials are very expensive and require long trial periods and very long review periods before a final

decision is made. So, in addition to a substantial research effort, an even more substantial developmental effort (in terms of qualified personnel, facilities and financial support) must be put forth before a biological product can be made available to the patient population. The research and development of a genetically engineered microbe for the production of a particular biological product is not the limiting factor in bringing the promise of modern biology to medicine and humanity. The time and capital-intensive elements required for the development of the large-scale processes and the regulatory pathway account for the delay in the delivery of useful products to the medical patient population. Of course, this long development time is obvious to those with any knowledge of the pharmaceutical drug industry, but the neophyte biotechnologists have had to experience this baptism.

The rapid pace of exciting biological research, with much of it related to medicine, should continue for at least another decade. Medically useful biologicals and other products derived from this basic research will flow through the developmental trenches and trickle through the regulatory pipeline to the needs of the public. This latter remark is not to be construed as criticism of the regulatory mechanism but rather as a statement of fact. One must take comfort in the fact that the safety and best interests of the public are paramount through all phases of the developmental and regulatory processes. For scientists seeking the excitement of understanding and for the public looking for new medical treatments, these are very promising times.

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Case Reports

Recurrent Asystole in a Child

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SEIZURES DUE to recurrent cardiac syncope in an otherwise healthy child are rare. In this report I describe the case of a 10-year-old boy with a structurally normal heart who had seizures due to recurrent sinoatrial pauses* with asystole.

Report of a Case

The patient presented to Riverton (Wyoming) Memorial Hospital having "passed out." He had been leaning against a well pump when he fell to the ground. His arms and legs jerked for five seconds and he was incontinent of urine and feces. He became alert immediately. Two weeks previously while camping, he had awakened, walked from his tent, lost consciousness while walking and had a seizure identical to that described above. He said he had had no premonitory symptoms or aura.

During the previous two months, he reported two episodes of rapid heart rate associated with chest pain lasting five minutes each. He did not seek medical attention for the first seizure described above, nor for the episodes of tachycardia.

He had previously been in excellent health. There was no family history of cardiac disease. A maternal aunt has recurrent seizures due to a stroke at age 19. At 8 years of age the patient had a left herniorrhaphy without complications. He had not been taking any medications in recent months.

On physicial examination he appeared thin and was pleasant, alert and cooperative. His temperature was 37.2°C (99.0°F), pulse rate 96 per minute, respirations 20 and blood pressure 96/60 mm of mercury. Supine and standing blood pressures were identical. There was a well-healed left herniorrhaphy scar. The scrotal sac was empty on the right. On cardiac examination he had normal heart sounds and no murmur. The remainder of the physical examination, including the neurologic examination, elicited no abnormalities.

*The term "sinoatrial pause" is preferred to "sinus arrest" because sinus arrest cannot be distinguished from sinoatrial block by standard electrocardiography.

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After admission to hospital, an irregular pulse rate of 52 per minute was noted. An electrocardiogram (ECG) and rhythm strip showed sinus arrhythmia, periods of sinus bradycardia and a wandering atrial pacemaker. The ECG findings were otherwise normal (Figure 1). Telemetry showed heart rates as low as 38 per minute during sleep, with PR intervals varying from 0.10 to 0.18 seconds with inconsistency in the configuration of the P wave.

Chest and skull x-ray films and electroencephalogram (EEG) showed normal findings. Laboratory studies gave the following values: glucose, 75, calcium, 9.5, and uric acid, 6.0 mg per dl; total protein, 7.3, albumin, 4.1, and globulin, 3.2 grams per dl; cholesterol, 174, blood urea nitrogen, 15, creatinine, 0.7, and total bilirubin, 0.6 mg per dl; alkaline phosphatase, 153, alanine aminotransferase (ALT, formerly glutamic-pyruvic transaminase), 7, aspartate aminotransferase (AST, formerly glutamic-oxaloacetic transaminase), 7, lactic dehydrogenase, 80, and creatine phosphokinase, 84 IU per liter; sodium, 143, potassium, 4.2, chloride, 109, and carbon dioxide, 24 mEq per liter; leukocyte count, 6,900 per μl with a normal differential count; hemoglobin, 13.5 grams per dl; hematocrit, 38.9%; erythrocyte sedimentation rate, 6 mm an hour, and platelet count, 241,000 per μl.

At 5 AM on the third day of his hospital stay, while being sleep-deprived for a second EEG, telemetry recorded profound bradycardia followed by prolonged asystole (Figure 2). After the development of asystole, the child was found in his chair having a generalized tonic seizure that ceased spontaneously within a few seconds. Shortly thereafter a temporary pacemaker was implanted. During the cutaneous infiltration of lidocaine in preparing to insert the pacemaker with the patient in the supine position, he had asystole for 20 seconds during which he again suffered a brief tonic seizure, terminated by the return of sinus rhythm.

Subsequently, cardiac evaluation of the patient was done at the Mayo Clinic in Rochester, Minnesota, including electrophysiologic studies, which showed normal sinoatrial node function, normal intrinsic heart rate (heart rate after autonomic blockade with atropine sulfate and propranolol hydrochloride), accelerated atrioventricular nodal conduction, dual atrioventricular nodal pathways without inducible reentry tachycardia and inducible sustained atrial flutter terminated by atrial pacing. Table 1 contains a summary of the sinoatrial nodal function. Neurologic and genetic consultants found no evidence of neurologic disease or an identifiable syndrome. Serum triglyceride values were elevated at 214 mg per dl. The serum thyroxine level

ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
EEG = electroencephalogram

was normal at 8.3 mg per dl. He was discharged from the Mayo Clinic on a regimen of propantheline bromide, 7.5 mg four times a day, and a low-fat low-carbohydrate diet.

Ten days later, a few seconds after blowing a flute at home, he had another syncopal attack despite the medication. A permanent demand ventricular pacemaker was implanted at Primary Children's Hospital, Salt Lake City, with the rate set at 50. Three months after pacemaker implantation he underwent right orchiopexy without complication.

Six months later, at school, the patient had 20 minutes of rapid heart rate associated with pallor, weakness and dizziness. He was admitted for 48 hours of inpatient observation and monitoring, which showed continued sinus arrhythmia, sinus bradycardia and normal pacemaker function, but tachycardia was not documented. Seven months after implantation, his demand rate was reprogrammed at 66 to alleviate recurrent symptoms of dizziness. He has suffered neither seizures nor syncope since implantation of his pacemaker.

Discussion

The differential diagnosis of generalized motor seizures must include cardiac syncope due to dysrhythmias even in children. Although sinus bradycardia and sinus arrhythmia are common in children, these findings must not be dismissed out of hand when faced with a history of cerebral dysfunction such as dizziness, fainting, memory loss or seizures.

This patient manifested many of the clinical signs and symptoms of the sick sinus syndrome—sinus bradycardia, sinoatrial pauses, syncope, seizures and a history suggestive of tachydysrhythmias. However, results of his electrophysiologic studies ruled out sick sinus syndrome due to intrinsic dysfunction of the sinus node by virtue of his normal response to atropine therapy with a brisk sinus tachycardia and his normal corrected sinus node recovery time. The sinus node recovery time is measured by subjecting the heart to rapid atrial pacing (starting at 120 beats per minute and increasing the rate by increments to 200) and measuring the longest interval from the last atrial pacemaker-induced spike to the onset of the first P wave (the "PP" interval). The sinus node recovery time exceeds the baseline PP in-

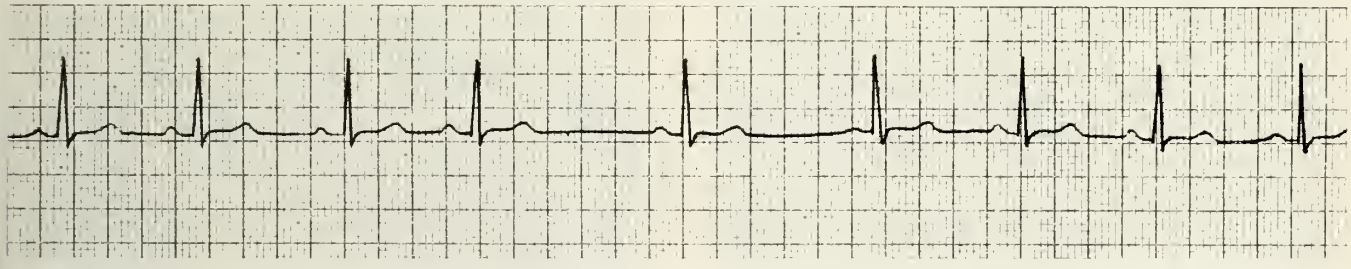

Figure 1.—Lead II rhythm strip shows sinus arrhythmia and varying configuration of the "P" wave (wandering atrial pacemaker). The QRS has been visually enhanced.

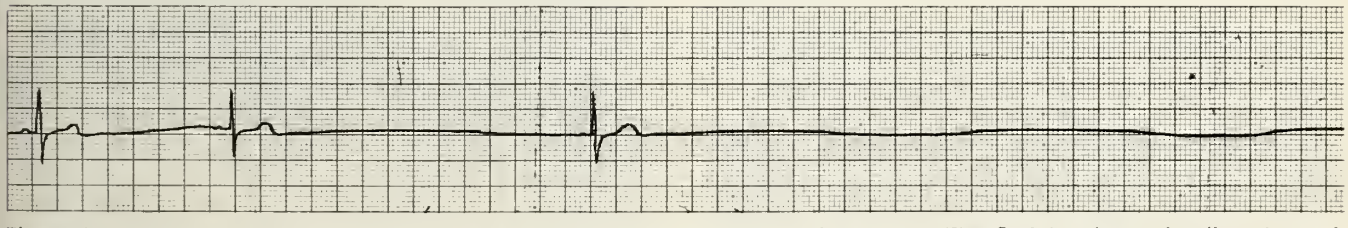

Figure 2.—Rhythm strip via telemetry shows severe sinus bradycardia and sinus arrest. The QRS has been visually enhanced.

TABLE 1.—*Summary of Sinus Node Function*

	Autonomic Blockade		
	Pre-Atropine Sulfate	*Post-Atropine Sulfate*	*Post-Atropine and Propranolol Hydrochloride*
Resting heart rate (beats/min)	88	138 (normal, 114)*	118
Longest sinus node recovery time† (msec)	970 (normal, 1,130)*		680
Longest corrected sinus node recovery (msec)	290 (normal, 525)‡		175

*Normal values taken from Yabek.[3]
†Atrial pacing ranged from 120 to 200 beats per minute.
‡The Mayo Clinic sets the upper limit of normal for the corrected sinus node recovery time at 525 msec.

terval in normal hearts, but is excessively prolonged when the sinus node is diseased or damaged. A prolonged sinus node recovery time strongly suggests decreased automaticity of the pacemaker cells in the sinus node or a delay in the exit of electrical impulses from the node into the atria due to disease, usually fibrosis, in the perinodal tissue. The computation of the sinus node recovery time—that is, recovery time minus the baseline PP interval—corrects for the fact that the sinus node recovery time is directly related to the baseline PP interval (the slower the resting heart rate, the longer the recovery time).

The normal sinus node recovery time, corrected sinus node recovery time and response to atropine effectively rule out an intrinsically dysfunctional sinus node as an explanation for the patient's findings.[1-9]

Vasodepressor, or vasovagal, syncope is a common phenomenon, but does not adequately account for this patient's symptoms. Vasodepressor syncope typically occurs in situations that a patient finds distasteful, is characterized by a presyncopal phase in which the patient anticipates losing consciousness and occurs in the standing or sitting position, only rarely in the recumbent position. Peripheral pooling of venous blood is the primary mechanism leading to hypotension. Vagal-induced bradycardia contributes to the decreased cerebral perfusion, but sinoatrial pause and asystole are not part of the syndrome.[10] Vagovagal syncope occurs when cardiac asystole occurs as a result of a reflex that is located entirely within the vagus nerve. However, this patient has no known lesion that might account for this phenomenon such as an esophageal diverticulum prone to distention, glossopharyngeal neuralgia, cardiospasm or a lesion in the larynx, pleura or peritoneum.[10]

In short, the patient in the case reported here does not seem to fit the description of patients previously classified as having one of the variants of cardiac syncope. Although it is doubtful that the dysrhythmia described is unique, an extensive search of the literature failed to reveal a case of recurrent sinoatrial pauses, asystole and seizures in an otherwise healthy child with a structurally normal heart and a normally functioning sinus node when tested electrophysiologically.

Autonomic imbalance appears to be at the root of this child's dilemma. Excessive vagal tone or diminished sympathetic tone at the sinus node could explain the findings as could excessive cholinergic sensitivity or diminished adrenergic sensitivity of his sinus node pacemaker cells. Aside from the fact that autonomic control of his sinus node could be blocked by administering atropine and propranolol, little is known of his intrinsic cholinergic control mechanisms.

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Peutz-Jeghers Syndrome With Cervical Adenocarcinoma and Enteritis Cystica Profunda

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THE PEUTZ-JEGHERS SYNDROME, one of the familial polyposes syndromes, is an autosomal dominant condition characterized by mucocutaneous melanin pigmentation and gastrointestinal polyps.[1,2] It is now recognized that there is a high risk that a distinctive ovarian tumor described as a sex cord tumor with annular tubules may develop in cases of this disorder.[3,4] Lately, however, a rare, well-differentiated adenocarcinoma of the cervix with a very poor five-year survival rate has also been reported with this condition.[5,6] An equally rare intestinal lesion known as enteritis cystica profunda is occasionally found in patients with Peutz-Jeghers syndrome.[7] This latter lesion is characterized by mucosal glands and mucinous cysts in the small and large bowel that penetrate the tunica muscularis. It sometimes involves the entire wall up to the serosa and, thus, has been mistaken for adenocarcinoma. We report the first case of Peutz-Jeghers syndrome that is associated with cervical adenocarcinoma and enteritis cystica profunda.

Report of a Case

The patient, a 29-year-old Latin-American woman, was admitted for weakness, dizziness and lower abdominal pain for one week. She gave a history of irregular and prolonged menstruation since the age of 16. Three months before admission, she had a spontaneous abortion of a 10-week-old pregnancy for which she required transfusion of two units of blood. She later had daily vaginal bleeding with lower abdominal pain for one month, culminating in this admission.

She was very pale, with a hemoglobin of 5.8 grams per dl and hematocrit of 17%. Pigmentation about the

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mouth, on the lips, buccal cavity and on the fingers and toes was noted. On pelvic examination there was an enlarged and tender uterus associated with a mass of the left adnexa. Copious blood-tinged mucus was noted in the vagina. Fractional endometrial and endocervical scrapings were obtained, which on histologic examination showed adenocarcinoma. A laparotomy was done because of the left adnexal mass, which turned out to be the enlarged cervix. Several intraluminal polypoid masses were found in the intestines, some large enough to cause obstruction, one of which was removed. A biopsy was done of a small intestinal serosal implant, which was reported as probable metastatic carcinoma from the cervix. After this, the patient had external pelvic irradiation with radium-implant therapy, followed by a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Two segments of small intestine with large polyps and serosal lesions were resected for further histologic analysis. Larger polyps were also removed singly together with their pedicles. A small mesenteric nodule not seen previously was excised together with two periaortic nodes.

Pathological Findings

The two segments of small intestine showed elevated, flat and oval nodules on the serosa similar to that from which a biopsy was taken during the first operation. Other serosal nodules were small, round and firm and located close to the mesentery. In each segment, just opposite the serosal nodule an intraluminal polyp was noted rising above the mucosa, 3 to 4 cm in its greatest diameter, with a very broad base and a coarsely lobulated surface.

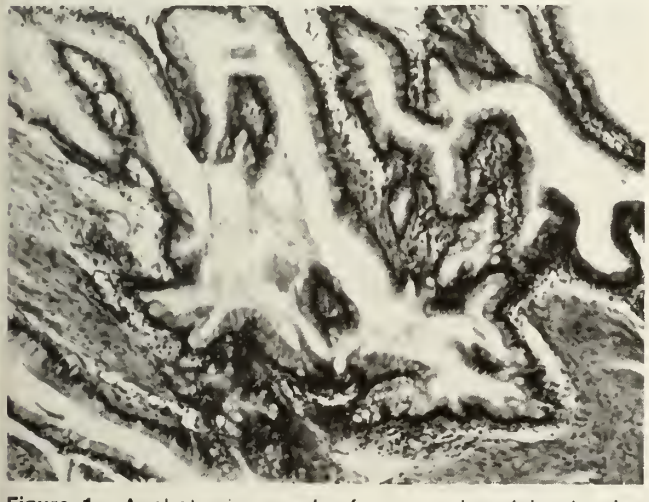

Figure 1.—A photomicrograph of a serosal nodule showing the columnar cell lining with numerous mucus cells and Paneth's cells sitting on the serosa. Note the absence of tumor fragments and signet ring cells in the mucin. (Reduced from magnification ×400.) (Klaus Lewis, MD, Department of Pathology, UCLA, reviewed the histopathology slides from the specimens of intestine and cervix.)

The other polyps submitted singly were round to oval with an average diameter of 3 cm. These polyps had a slender pedicle, the longest of which was 2 cm in length. Microscopically, the polyps were characterized by arborization of the tunica muscularis and covered by mucosa composed of columnar absorptive cells, well-differentiated glands containing Paneth's cells and mucus cells. The underlying muscularis mucosa and muscular layer were penetrated by dilated glands up to the serosa. This serosal lesion, which was mistaken for carcinoma implants on the first operation, showed similar mucosal cells and glands but oriented towards the peritoneal cavity (Figure 1). In addition, greatly dilated glands containing mucus were seen together with focal areas of calcification and ossification in the muscular layer, serosa and pedicles of the polyps.

The uterus and cervix were symmetrically enlarged and the entire specimen measured 14 by 9 by 7 cm. The cervix and lower half of the body were firm and grayish white, which on microscopic sections showed an extremely well-differentiated mucinous adenocarcinoma. The glands were lined by a single layer of endocervical-type epithelium with minimal atypia, making it difficult to distinguish from normal endocervical glands. However, some abnormalities in the shape, size and number of these glands, together with their deep penetration into the cervix and myometrium, made their malignancy obvious. The ovaries and tubes showed no abnormalities. The 2-cm mesenteric nodule showed metastatic adenocarcinoma. None of the periaortic nodes showed malignancy.

Discussion

This patient presented with the classical manifestation of cutaneous and oral pigmentation with multiple hamartomatous polyps in the intestinal tract. In addition, a rare, well-differentiated mucinous adenocarcinoma of the cervix was found. "Adenoma malignum" describes this highly differentiated tumor due to its deceptively innocent histologic appearance but with a highly aggressive character.[5,6] Of six patients reported to have this condition, only two are alive after five

TABLE 1.—*Peutz-Jeghers Syndrome and Additional Pathologic Lesions*

Affected Organs	*Pathologic Lesion*	*Reference*
Uterus	Adenoma malignum, or well-differentiated mucinous adenocarcinoma of the endocervix	McKelvey and Goodlin, 1963[5] McGowan et al, 1980[6]
Ovary	Sex cord tumor with annular tubules (SCTAT)	Clement et al, 1979[3] Costa, 1977[4]
	Sex cord stromal tumors with sexual precocity	Young et al, 1983[10]
Intestines	Enteritis cystica profunda	Kyriakos and Condon, 1978[7]

years of observation.[6] This tumor not only metastasizes early but is unresponsive to conventional treatment. Our patient was found to have a metastatic omental nodule just four months following completion of radiation treatment.

Another rare lesion was found in the small intestine in this patient in close association with the polyps. This is called enteritis cystica profunda[7] and is characterized by glands that penetrate deeply through the wall even up to the serosa, as seen in this case. This serosal lesion presented a dilemma then as to whether it represented a malignant invasion from the polyp as previously described[8,9] or a metastatic implant from the adenocarcinoma of the cervix. However, the irregular distribution of the glands and cysts with normal-appearing glandular epithelium containing mucus and Paneth's cells are features suggestive of its benign nature. Furthermore, the characteristic features of mucinous adenocarcinoma, namely, tumor fragments and signet ring cells in the tissue, are absent. While the pathogenetic mechanism of this lesion is uncertain, we share the opinion of others that these penetrating glands are hamartomatous growths in the reverse direction towards the serosa, in addition to their usual growth towards the lumen to form a polyp.

Recently, two unusual ovarian tumors are reported to belong to this syndrome,[10] which are distinctive from the various ovarian tumors previously reported.[3,4] The earlier tumors exhibit both simple and complex ring-shaped tubules, earning the name sex cord tumor with annular tubules.[3,4] These distinctive tumors, however, have a more varied histologic pattern and are associated with sexual precocity.[10]

Thus, this syndrome appears to have expanded lately to include various significant lesions in different combinations. Patients with this condition, therefore, should be assessed carefully in the light of our knowledge of the various associated pathologic features (Table 1). Our patient presented with two of these rare lesions consisting of enteritis cystica profunda and well-differentiated adenocarcinoma of the cervix, which had never been described before in one person.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Treatment of Rattlesnake Bites

To the Editor: In the correspondence on rattlesnake bites in the January 1984 issue, Dr A. M. Butner appears to imply that the venom of the northern Pacific rattlesnake, *Crotalus viridis oreganus (Cvo),* is substantially different and less toxic than that of the southern Pacific rattlesnake, *Crotalus viridis helleri (Cvh).*[1] Unfortunately, there are no experimental or clinical data to support such a contention. The LD_{50}s for the venom of the two subspecies are identical, as are their separations by electrophoresis, their patterns on isoelectric focusing, ELISA (enzyme-linked immunosorbent assay) findings and all physiopharmacological measurements to which the two venoms have been subjected. There is as much difference in the composition of the venoms of individual snakes of one subspecies as there is between the venoms of the two subspecies. In no way can the two subspecies be divided on the basis of their venom. In fact, they are divided only by an imaginary geographical line running from Lebec-Shandon–Cape San Marin in Kern and San Luis Obispo counties, California, and by indifferent terminal rings on the tail. Having treated well over 300 patients bitten by these two subspecies, I feel I would be at a loss to distinguish any clinical differences in either the symptoms and signs of envenomation, or the severity of poisoning following the bites of the two subspecies.

I think Dr Butner has just been lucky (which has been my experience for the same area) in that the patients he has reported on have not been bitten by large members of the subspecies. The number of bites by *Cvo* is certainly far less than that for the southern subspecies. However, I am sure that Dr Butner is aware that there have been deaths due to the bites of *Cvo.* Over the past 30 years I have consulted on numerous cases in which severe tissue changes ensued following the bite of this subspecies, principally consultations from northern California and Oregon.

I agree with Dr Wingert[2] that the grading system used by Dr Butner is not applicable to bites by the western species of rattlesnake, and is slowly losing favor elsewhere. I am rather surprised that Dr Butner states that the grading system which Dr Wingert refers to "does not lend itself to a sensitive adjustment of antivenin dosage as the toxic state progresses," for that is the *very* reason that that system was developed. Dr Butner's statement is almost the opposite of the argument I presented in my book[3] for *not* using the system he suggests.

> The grading methods of 0 or 1 through 4 or 5, which were suggested and used many years ago,[4,5] are precarious . . . they are usually based on a few selected symptoms or signs, and these are often measured at 12 hours following the bite. The physician should base his diagnosis . . . on all clinical manifestations, including changes in the blood cells and chemistry, changes in motor and sensory function. . . .[3]

I feel the "numbers system" is useful only to those who know what their own numbers mean. My experiences in the courts would seem to indicate that there is no common definition or agreement on these numbers for grading.

Finally, it is to be hoped that clinicians will never base their treatment on the "virulence of local reptiles." We are treating patients, not reptiles, and it is the patient's symptoms and signs and the severity of the poisoning to which our attention should be directed.

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Ergonovine-Induced Chest Pain Not Due to Coronary or Esophageal Spasm

To the Editor: We would like to comment on the informative paper by Lieberman and co-workers, "Ergonovine-Provoked Esophageal Spasm During Coronary Angiography," in the March issue.[1]

We concur with the concept of performing simultaneous coronary angiography and esophageal manometry during provocative ergonovine maleate testing. We consider an important observation to be the chest pain induced by ergonovine in patient 9 in the current study, accompanied by neither angiographic nor manometric changes at the time of pain. We have had similar findings in three patients, although two of them had minor underlying manometric abnormalities not exhibited at the time of chest pain following ergonovine. Cardiac metabolic studies were not carried out but there was a rise in systemic arterial pressures and a

slight elevation of left ventricular end-diastolic pressures. Our three cases, in conjunction with the case reported by the authors, suggest that a different mechanism is responsible for the severe chest pain. This may represent angina pectoris induced by ergonovine maleate due to a reduced vasodilatory reserve of the small coronary arteries,[2] an occult cardiac disease process or chest pain of extracardiac origin stimulated by ergonovine in a yet-undefined manner. It is hoped that further investigators will define this separate mechanism of chest pain.

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Can an Aorta Be Ectatic?

To the Editor: I noted Dr Rosen's comment[1] on our use of the term "ectatic" in our Medical Progress article "Abdominal Aortic Aneurysms."[2] He is quite right that "ectasis" or "ectasia" is defined as "distended" or "stretched" in *Dorland's Illustrated Medical Dictionary* —thus the common usage in "bronchiectasis," "mammary duct ectasia" and the like. Most of those involved with vascular diseases, however, understand "ectatic" to mean "tortuous" or "uncoiled," and this is a usage validated, in part at least, by the *Oxford English Dictionary,* which defines "ectasis" as "extension or stretching out" (to be fair, a second meaning for "ectasis" in the *OED* is "a state of dilatation").

While vascular surgeons and angiographers will probably continue to use the term "ectasia" to describe the tortuous, normal-caliber aorta, the purist in us agrees enough with Dr Rosen to grant that we will endeavor to stick to "tortuous" or "uncoiled" when that is what we mean.

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* * *

To the Editor: In his recent letter to the editor, Rosen objected to the use of the word "ectatic" as a synonym for "tortuous" or "uncoiled" (as in, "the thoracic aorta is ectatic").[1] He rightly pointed out that "ectatic" means distended or stretched. Like Rosen, I initially found this use of ectatic jarring, but I believe it is etymologically justified.

Morphologically, the fibers of the aging thoracic aorta stretch. This results in an increase in the diameter of the thoracic aorta (aortic dilatation). However, stretching also occurs in the *longitudinal* axis of the aorta, resulting in elongation. The thoracic aorta is in essence a fixed loop within the chest, and when elongation occurs, the arch (the top of the "loop") is not displaced superiorly. Rather, the additional length is taken up by displacement of the ascending arch into the posterior aspect of the left hemithorax.

Because this aortic elongation is the result of "stretching," it fits the definition of the word "ectatic."

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Hyperbaric Treatment

To the Editor: I was disturbed by the article "Homonymous Hemianopia Due to Cerebral Air Embolism From Central Venous Catheter"[1] in the April issue.

In both cases reported no mention was made about the primary treatment of cerebral air embolism, and that is hyperbaric treatment, preferably in a double-lock chamber in which the patient is subjected to pressure equivalent to 165 ft of water.

Had these patients been subjected to the US Navy Table 6A treatment when the diagnosis was suspected, it is possible that neither one would have been left with any neurological residual.

If a physician does not know where the nearest hyperbaric chamber is located, one should call DAN (Diving Accident Network), (919) 684-8111. They will be able to identify the nearest available chamber anywhere in the United States.

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Patient Responsibilities

To the Editor: I wish to share with the journal's readers my feelings of frustration and indignation while taking care of a very sick patient. Is it that we are losing faith, the most important part of healing?

A middle-aged man was admitted to hospital under my care with preceding history of "so-called seizure." He had arrived in Las Vegas the day before. On detailed questioning of the family and the patient, no significant past medical history was elicited. There was direct questioning about any history of alcohol consumption (including beer, because some people do not think of beer as an alcoholic beverage). Findings on physical examination were unremarkable, as were results of laboratory tests and a computed tomographic scan of brain. Even with no definite history of alcohol consumption, he was also observed for withdrawal symptoms (unpublished observations: alcohol-related syncope or near-syncope tops the list of causes of "passing out" in Las Vegas).

On the third day, profound confusion, vivid hallucinations, tremors and agitation developed—full-blown delirium tremens. At this time the mother of the patient walked up to me and said, "Yes, Doc, he is an alco-

holic." I asked, "Did he ever have this type of withdrawal symptoms before?" "Yes," she replied. I felt frustrated and disgusted. Do we physicians have to learn some tricks in lie detection, too? I cannot understand why those coming to a hospital or to a doctor for help would lie (exceptions are the addicts whose motives at the outset are clear). We physicians start working with patients with a feeling of mutual trust and understanding. If one party (or the close family of the same) is lying and hiding information, how are you expected to react and function? A clinical history, I learned, is most important in diagnosis—or should I say a "correct history"? Public education about this is extremely important.

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More on Gravity Inversion

To the Editor: During the past year gravity inversion therapy has attracted considerable attention. The popular press has publicized gravity inversion boots, devices constructed of metal and foam rubber that clasp around the ankles, allowing one to hang in the completely (−90 degree) inverted posture from a stationary horizontal bar. In addition, there are other gravity inversion modalities, such as the gravity oscillator which not only allows the user to invert but to control body position while lying on an oscillating plank that allows one to rotate from an upright to a totally inverted posture with little effort. We chose the latter method for our latest investigation in this area.

Gravity inversion equipment was designed by Robert Martin, MD, in the 1960s to aid patients in relief of low back pain by utilizing gravity and their own body weight to decompress the spine and vertebral discs through inversion.[1] In our first series of studies we statically inverted subjects for three minutes and noted elevations in systemic blood pressure, intraocular pressure, central retinal artery pressure and pulse rate.[2,3] In these studies we first examined healthy medical students, and in other studies statically suspended borderline hypertensive volunteers for a three-minute period of inversion.[4] We interpreted our initial evaluations as a risk to specific patient populations (those with uncontrolled hypertension and those with uncontrolled glaucoma).

In view of our new work in this area, however, we have modified our opinion of the safety of gravity inversion therapy for healthy participants. We subjected 20 healthy volunteers with no history of glaucoma or hypertension to 15 minutes of oscillation on the gravity guider oscillator. Subjects were allowed to control their own rate of oscillation and performed from 80 to 150 complete oscillations during the 15-minute period, with each oscillation lasting for at least six seconds. Measurements were taken at rest, seated and then after 15 minutes of oscillation. Pulse rates were measured from the right radial pulse. Blood pressure was measured with an aeroid sphygmomanometer with the right arm supported laterally at the heart level for all measurements. Intraocular pressure was determined utilizing the MacKay-Marg model 12 applanation tonometer. Ophthalmodynamometry was used for central retinal arterial pressure measurements.[5] All measurements were taken in the (−90 degree) inverted position.

We found the systemic blood pressure to decrease from 122/80 mm of mercury in the upright position to 120/78 mm of mercury after 15 minutes of oscillation. Pulse rate dropped from 76 to 72 in the same time. Intraocular and central retinal arterial pressure increased in a similar fashion to static inversion but of less magnitude. All the above results were statistically significant. None of our subjects had the discomfort of static inversion (headaches, nausea, head congestion, dizziness). They all reported a calm, relaxed feeling of well-being and tranquillity, which was associated with progressively diminished blood pressure and pulse rates below resting levels. The hydrostatic increase[3,4] in intraocular and central retinal artery pressure balance and protect each other with a "balloon pressing against a balloon within a box" effect.[5] Each prevents the other from damage.

The risk of stroke expressed in previous studies has been grossly exaggerated by the media. To date there has not been a single case of reported stroke or cerebrovascular accident associated with all forms of inversion therapy during the last 15 years they have been popular. Protection against brain hemorrhage may be afforded by the concomitant increase in cerebrospinal fluid, as well as the closed box system of the skull cage, previously demonstrated in the aerospace literature,[6] with the ability of unprotected laboratory animals to withstand negative 15 Gs of pressure. In addition, blood pressure elevations of 450/310 mm of mercury have been recorded in persons undergoing extensive weight training in the upright posture, which far exceeds any results we have encountered with gravity inversion equipment.[7]

In summary, we conclude that the oscillating gravity guider device is a safe manner of utilizing gravity inversion therapy. In addition, it is suggested that all these devices be utilized by keeping in motion to avoid the congestive effects of static hanging.

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Informed Opinion

A Physician Looks at DRGs

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With astonishing swiftness, House/Senate conferees, on March 24, 1983, finalized the 1983 Social Security Amendments, including the Medicare Prospective Payment System, and the bill was signed into law April 20, 1983. On September 1, 1983, the Health Care Financing Administration published interim final regulations, and on January 3, 1984, published final regulations implementing the Medicare Prospective Payment System (PPS). The regulations established Diagnosis Related Groups (DRGs) wherein the approximately 5,500 hospitals to be included in this system will receive a predetermined flat payment per case based on the patient's diagnosis. These DRG prices are payment in full and are not negotiable. In this system, hospitals are paid for their outputs (treated cases) rather than for their inputs (services or days of care).

Before the passage of the 1983 Social Security Amendments, which established the National Medicare Prospective Payment System using DRGs, the DRG system had been used for only two years in 26 hospitals in New Jersey, and even fewer in Maryland. This rapid acceptance of DRG payment in the absence of much experience argues for a careful look at its implications. The incentives of the DRG system have implications for the efficiency and quality of care delivered to Medicare beneficiaries.

The theory is that all hospital patients assigned to the same DRG represent a homogeneous group. They are similar not only in terms of the broad clinical description of their illness, but also in terms of their length of stay in the hospital, the resources they consume and the cost of their treatment. From now on, the meter is running and hospitals have to keep an eye on that meter as patients are cared for. If a patient is treated for a cost under the predetermined payment, the hospital keeps the savings. If the treatment costs are more, the hospital must absorb the loss. The job, therefore, is to keep the cost under the price, and this puts hospitals under overall pressure to restrain consumption of resources. There will be strong economic incentives to minimize a patient's length of stay, as well as incentives to minimize intensity of care or volume of services.

Physician-Hospital Cooperation Needed to Control Costs

The cost control incentives under DRGs are comprehensive. The hospital must control input costs—labor, capital and supplies—and also seek to optimize clinical case management techniques. The hospital that can be a tougher manager by holding the line on personnel growth will enhance its profit margin. Holding down ancillary expenses per inpatient admission and increasing outpatient preadmission testing will maximize profits. Incentives are created for careful discharge planning and the provision of care in a nonacute setting.

The ability of a hospital to respond to prospective payment incentives depends on the ability of a hospital administration to transmit these incentives to the medical staff. The prospective pricing system puts hospitals at risk for the things that doctors do. The DRG system, as it is now constructed, contains no direct incentives for physicians to control costs. The physicians, because they control the allocation of a significant proportion of resources in hospitals, have a central role to play in determining just how well the system works. But, physicians remain wary. The changes that are occurring are in an unknown direction. This new system is perceived by physicians as inevitably causing loss of both financial and judgmental independence as well as moral commitment. It is feared that individuality and the intimate patient/physician relationship will become lost in this highly organized setting. What concerns most physicians is the "bottom line mentality" that ignores quality of care and access for the sake of reducing costs.

Implementing the System

Although hospitals will be paid under the system beginning with their first cost-reporting periods on or after October 1, 1983, the DRG system will be phased in over a three-year period. The country will be divided into nine regions, each with an urban and rural rate,

(Lang HL: A physician looks at DRGs [Informed Opinion]. West J Med 1984 Aug; 141:248-255)

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ABBREVIATIONS USED IN TEXT

DHHS = Department of Health and Human Services
DRG = Diagnosis Related Group
ICD-9-CM = *International Classification of Diseases—9th Revision—Clinical Modification*
ICDA-8 = *International Classification of Diseases Adopted—8th Revision*
MDC = major diagnostic category
PPS = Prospective Payment System
PRO = Peer Review Organization

consisting of a labor and nonlabor component. Over the three-year transition period the Department of Health and Human Services (DHHS) will move toward uniform national urban and rural rates phasing out the regional differences. This transition period will involve not only the blending of rates, but further regulatory amendments and potential statutory changes. The new system covers all hospitals except rehabilitation and psychiatric hospitals, children's hospitals, long-term care hospitals, distinct psychiatric and rehabilitation units and hospitals in states that have a waiver for the PPS (New Jersey, Massachusetts, Maryland and New York).

For fiscal year 1984 the system will base 75% of a hospital's payment on hospital-specific historical costs and 25% on DRGs. The DRG rate portion of the payment will be divided between the national DRG rate and a regionally adjusted amount based on labor costs for the US Census District in which the hospital is located and an urban/rural differential. In fiscal 1985 half of the payments will be DRG based (37.5% regional average price; 12.5% national average price) and half hospital specific. In 1986 DRGs will set 75% of the payments (37.5% regional average price; 37.5% national average price) and historic cost will be the basis of 25%. In 1987 all Medicare inpatient payments will be made on the basis of DRGs. Payment in 1987 will be based totally on the urban and rural national average price for each DRG adjusted for differences in area wages. At this point the hospital's individual cost performance will have no impact on the DRG rate.

So, rate setting under the PPS will reduce the influence of the hospital's own cost performance on its DRG rate from 75% in the first year to zero in the fourth year. Ultimately, then, the important consideration is going to be a hospital's own performance and efficiency relative to other hospitals in the region and the nation. Over time it is expected that the fixed rate will be reduced, and the concern is that the regulators will reintroduce regulation and impose spending caps to keep costs at the new low levels, rather than to allow normal market equilibrium to keep competitors and costs in check.

Shortfalls Expected by Most California Hospitals

An analysis of this new PPS shows that with one exception all types of California hospitals will suffer more shortfalls than bonuses—especially as the system shifts from regional to national DRG rates. For 1984 some 72% of California hospitals will have shortfalls totaling $202 million less than their estimated costs; the remaining 28% will receive bonuses of $28 million. But, if the fourth year of prospective pricing, which uses only national DRG rates, were in effect, 66% of California hospitals would have a total shortfall of $579 million, while the rest shared bonuses of $153 million. Only the group of hospitals with fewer than 50 beds would have bonuses exceeding their shortfall.

The figures show a shift of funds from one part of the country to another. If the fourth year were in effect, the big losers would be the Pacific states (particularly California) with shortfalls of $614 million and bonuses of $295 million, and the two North Central regions with total shortfalls of $1.299 billion and bonuses of $485 million. The big winners would be the South Atlantic states with shortfalls of $452 million and bonuses of $507 million and the East South Central states with shortfalls of $147 million and bonuses of $217 million.

Background of DRG Concept

The DRGs were initially developed at Yale University in the early 1970s by health services researchers interested in defining expected lengths of patient stays so that utilization review activities could be focused on atypical patients. Length of stay was used by researchers as a surrogate for resource consumption, and within each DRG, length of stay is assumed to be similar. However, length of stay by itself is not an accurate indicator of total patient treatment costs. This becomes more evident when we consider different treatment patterns, including the many different ancillary procedures possible that may occur with different patients in the same DRG.

One analysis of a random sample of cases in 12 high-volume DRGs in New Jersey hospitals found that 13.6% of discharges had a length of stay more than two times the average of cases in that category. DRGs do not in fact group patients well according to a hospital's legitimate expenses for taking care of them. In one New Jersey hospital, charges ranged from $1,140 to $3,900 in one DRG and from $2,900 to $8,700 in another.

The original DRG used *cause of disease* as the basis of grouping ICDA-8 *(International Classification of Diseases Adopted—8th Revision)* codes in 83 major diagnostic categories (MDCs) according to similarities in anatomy, pathophysiology or clinical management. It then subdivided these MDCs into 383 DRGs using a statistical splitting process that grouped patients with similar diagnoses and length of stay.

This system has been superseded by an entirely new set of DRG definitions using ICD-9-CM *(International Classification of Diseases—9th Revision—Clinical Modification)* codes. This DRG classification system was based on 1.4 million records selected from a na-

tionally representative sample of 332 hospitals participating in a Commission on Professional and Hospital Activities abstracting service. This new system assigned ICD-9-CM codes to most MDCs according to which of the *body's organ systems* was affected. All ICD-9 codes were allocated to 23 MDCs based on the body system affected. In this new DRG system the initial division of most MDCs was the presence or absence of an operating room procedure. This resulted in a medical and surgical partition of each MDC. Subsequent splits were made to reflect variation in diagnoses, secondary conditions, treatment and patient age. In all, five variables were identified as important predictors of length of stay and cost behavior:

1. *Specific operating room procedure.* The most resource-intensive operating room procedure on the patient's record is used to assign the patient to a surgical DRG.
2. *Principal diagnosis.* This is defined as a condition established after study to be chiefly responsible for the admission of a patient to the hospital.
3. *Age.*
4. *Presence of substantial complications.* A "complication" is a condition other than the principal diagnosis that arises while a patient is in the hospital.
5. *Presence of substantial comorbidities.* A comorbidity is a condition existing before a patient's admission to the hospital.

Complications or comorbidities were considered "substantial" if, when present as a secondary diagnosis, they were likely to increase the length of stay by at least one day in about 75% of the patients.

The Yale research team determined that the additional resources used by an elderly person were about the equivalent to those of a patient with substantial complications or comorbidities. Therefore, a new decision variable was created to group together patients who either had a substantial complication or comorbidity or were age 70 or older. The researchers felt that this split was an appropriate determinant of resource use on both statistical and financial grounds.

After all this grouping and splitting, there are 467 categories. There are three additional DRGs established for patient abstracts not groupable into any of the 467 DRGs:

1. DRG 468—unrelated operating room procedure to a given DRG (for example, a patient is admitted for cataract surgery but has a myocardial infarction on the table and requires a coronary bypass). DRG 468 represents a discharge in which all operating room procedures present on the discharge record are unrelated to the principal diagnosis.
2. DRG 469—principal diagnosis invalid as the discharge diagnosis.
3. DRG 470—discharge with invalid data. The record does not meet the criteria for any DRG.

Determining DRG-Based Payments

The national standard price for each DRG will be set annually and updated each year. For fiscal year 1984 and 1985, Congress required the Department of Health and Human Services to increase the rates by the hospital market basket of goods plus 1%. The "market basket" approach attempts to determine proportionately the types of goods and services an institution will use in the course of a business cycle. A provision will thus be made to account for the weighted average increase in the cost of these goods and services by using published proxies such as consumer price index (CPI) and product price index (PPI) to determine the inflationary experience.

This national standard price is the product of two cost measures: (1) a relative DRG price index (cost weight) and (2) a national representative cost per discharge. The DRG weighting factors are based on average standardized costs for each DRG developed from cost data from hospitals. The average standardized cost for each of the 467 DRGs was calculated by adding the standardized adjusted costs for all cases in the DRG and dividing that amount by the number of cases classified in the DRG. The average standardized cost for each DRG was then divided by the overall average standardized cost to determine the weighting factor. Each weighting factor reflects the average cost across all hospitals of treating cases classified in that DRG relative to other DRGs. It describes the relative costliness of treating different types of Medicare cases.

These weights were constructed by using the 1981 MedPar (Medicare Provider Analysis and Review) data and non-Medicare discharge record data from Maryland and Michigan hospitals for the same period. The MedPar file is a 20% sample of Medicare claims from short-stay hospitals for Medicare patients with Social Security numbers ending in zero or five in 1981.

The national representative cost per discharge is determined by using the 1981 Medicare cost reports and 1981 discharge file. The Medicare cost report contains information on direct capital, medical education costs and operating costs, and is the information institutional providers submit in order to be reimbursed for services provided to Medicare beneficiaries. The discharge file provides the data for the number of Medicare cases treated by a hospital during a given calendar year.

The price index is a series of relative prices while the national representative cost per discharge is a single dollar amount that would set the overall DRG price level. When the relative price index is multiplied by the national representative cost per discharge, a set of national standard DRG prices is obtained. After the standard DRG prices are adjusted for area wage differences to create hospital area prices, there is a specific payment price for each DRG.

Adjustments Permitted in Certain Situations

Teaching hospitals will receive a special facility adjustment. Direct costs of medical education, basically

the salaries of residents and interns, will continue to be paid on a reasonable cost basis. Indirect costs of medical education, such as the additional laboratory tests, will be paid at twice the TEFRA (Tax Equity and Fiscal Responsibility Act of 1982) 223 limits. Thus a typical teaching hospital may receive an additional 12% revenue on top of the total DRG reimbursement. There are also special facility adjustments for rural referral hospitals (paid at the urban DRG rate), sole community hospitals (75% hospital specific and 25% regional rate) and cancer hospitals (may elect to be paid on a reasonable cost basis rather than PPS).

There are also a series of special financial adjustments available:

1. *Capital costs.* Until 1986 previously incurred capital-related costs (interest, rent and depreciation) will be "passed through" and be reimbursed on a reasonable cost basis. By September 1984 the Secretary of Health and Human Services must complete an evaluation of methods by which capital-related costs, including return of equity, can be incorporated in the prospective pricing system. Congress is seeking to protect against unlimited and uncontrolled capital spending by hospitals and the inevitable operation consequences in future years that might result if capital costs were simply passed through. Because of the uncertainty surrounding Medicare future capital payment policy, obtaining bonds, loans and mortgages will be difficult. Significant financial pressure on the hospitals may lead to reduction in capital improvement, new equipment purchases and basic maintenance. This fixed price system does not provide for the replacement of capital in an inflationary economy, the development of new technology or the accumulation of working capital reserves. How capital costs are treated will affect the use of medical technology. Technology diffusion—that is, the rate of adoption of innovations for the support and improvement of medical care—is one of the areas that is likely to be affected as hospitals attempt to reduce their costs per case.
2. *Outliers.* Outliers are defined as cases involving an unusually long stay (day outlier) or cases in which the costs are above the DRG rate (cost outlier). A case will be determined to be a day outlier if the number of days in the stay exceeds the mean length of stay for a discharge within that DRG by 20 days or 1.94 standard deviations, whichever is less. For those cases determined to be day outliers, Medicare will pay 60% of the per diem. However, this 60% will be multiplied by the applicable federal percentage set at 25% in the first year, 50% in the second year and 75% in the third year and, starting in year four, 100% of the 60% will be paid.

   A cost outlier would be based on a hospital's request for outlier payment in situations where the cost of covered services exceed $12,000 or 1.5 times the federal rate for the DRG, whichever is greater. Medicare will pay 60% of the difference between the hospital's adjusted cost for the discharge and the cost outlier threshold. Again, the 60% rate will be phased in during the transition period using the same federal percentage as described for day outliers.

Continuing Adjustments Needed to Refine System

Although the ICD-9-CM DRGs are better able to group patients according to similar illnesses and resource use, the new system still has weaknesses. DRGs reflect the state of medical practice at the time of their development; technological advances are not reflected in the groupings. If an effective but more expensive treatment is developed for a particular condition, hospitals may not be able to provide it since their DRG payment would be limited to the amount established considering current treatment patterns.

If DRGs are to be used as a predictor of patient care costs, better financial information must be incorporated into the data base. The Yale research team used hospital charges as an approximation for actual costs in constructing the revised DRGs. Because charges do not represent the true costs of treating a patient, some DRGs may not actually group patients according to resource consumption. The data base that was used to define the DRGs consisted of discharge abstracts. One recent study by the Institute of Medicine, a branch of the National Academy of Sciences, indicated that errors up to 35% are being made in diagnosis and procedure coding.

Another weakness of DRGs is that they do not distinguish among patients with different levels of intensity or severity of the same disease or disorder. Although age and secondary diagnosis correlate with severity of illness, they can differentiate patients only within an MDC and not within a DRG. Such variables as condition at time of admission, diagnosis or socioeconomic status may also influence resource consumption but are not included in the decision model.

Congress included in the DRG legislation the formation of an independent, 15-member prospective payment assessment commission to make recommendations to the Secretary of DHHS concerning updating payment rates and recalibrating DRG classifications to take new treatment modalities into account. The commission will first consider the DRG classifications and weighting factors in fiscal 1986. Subsequent recommendations will be made every four years. The commission could make recommendations that could determine if new higher paying DRG categories would be created to accommodate new expensive technologies.

Are the DRGs applicable nationwide? Blue Cross of Western Pennsylvania, using the Yale methodology, analyzed 600,000 cases from 90 western Pennsylvania hospitals to see whether the same methodology could be applied to another region of the country. The results show that the same DRGs do not apply to all regions

of the country and, in fact, unique DRGs will have to be developed for each major metropolitan area.

Another limitation of the existing DRG system relates to standby requirements for patients. DRGs are based on discharge data and consider *what happened* to the patient. *Potential* medical complications that could have materialized for a patient were not considered. For example, if a high risk pregnancy results in a normal delivery, the DRG system would classify the patient as a normal delivery; thus, the classification of that patient gives no recognition to the special services and equipment needed in the event that the risk materialized. Therefore, while the patient is classified in the correct DRG (considering the length of stay), the DRG classification does not accurately reflect the resource requirements necessary to provide care and treatment for that patient.

A Key Professional Concern: Preserving Quality

The most threatening aspect of the DRG system is its impact on quality of patient care. For the purposes of Medicare, the hospital's operations are reduced to 467 "products." The DRG system establishes a set of hospital "product lines" for which "retail prices" will be known. The hospital must reduce costs to the level of the retail price (DRG) or lose money. One way of looking at this system is that a patient is now billed as a complete finished product (one appendectomy, one mitral valve replacement and the like) rather than being billed for the total of goods and services the patient consumed while in the hospital. There is a real risk that the product will be cheapened to reduce costs, which will sacrifice patient care.

According to Peter Drucker, the originator of management by objectives—"service institutions do need efficiency—that is, control of costs; but above all, they need effectiveness—that is, emphasis on the right results." The right results for hospitals are saving lives and getting people well. The problem with DRGs is that they simply measure cost efficiency and do not consider whether or not a patient is cured.

Since the economic incentive for a hospital is to find a way to provide services below the DRG reimbursement rate, this may lead hospitals to select a "mission" to provide those services at which it can make a profit and discard those services which are not profitable. Since, as was previously mentioned, there can be significant variances in the cost of treating patients in the same DRG, this creates an economic incentive for hospitals to treat patients whose costs are lower than average within a given DRG. Therefore, those patients whose illness is likely to result in resource consumption in excess of the average for the DRG may have problems gaining access to hospital care. In essence, hospitals will no longer provide all services to all people.

Hospital management will develop skills in "pruning" product lines—weeding out unprofitable products and promoting its profitable products. This review of the product line will affect decisions on equipment acquisitions, staffing levels and medical staff composition. Per case payment introduces incentives for cost control in hospitals, but it also has potential negative implications for quality of care and access to care. The incentives in DRG payment for hospitals to potentially manipulate case load, overadmit patients, discharge patients too early and underprovide ancillary technologies argue for safeguards in the form of quality and utilization review. Utilization review will be necessary to avoid costly increases in both admissions and readmissions and quality audits will be necessary to protect patients from the underprovision of technologies and too early discharge. Review processes that recognize the balance between cost and quality become critical under the DRG payment.

Federal Regulations Mandate "Peer Review"

The federal government's concern for "quality" was addressed in the regulations. Beginning October 1, 1983, review must be done by a "medical review agent." Until October 1, 1984, this agent may be a Professional Standards Review Organization (PSRO), a Peer Review Organization (PRO) or a fiscal intermediary. After October 1, 1984, each hospital must have contracted with a PRO in order to receive payment under Medicare.

The following types of review are mandated: (1) appropriateness of admission (based on a sampling), (2) all outlier cases and (3) random sample of discharges on a quarterly basis.

In reviewing day outliers, the review agent must approve the admission, the number of outlier days and the validity of the diagnosis and procedural coding. In reviewing cost outliers, the review agent must determine the following: the admission was medically necessary and delivered in the most appropriate setting; services were actually rendered, ordered by the physician and not duplicatively billed, and coding was correct.

Medical necessity was added as a review criterion for length of stay outliers. The overall subject of review was also expanded. Where the interim final rule required review of "the quality of its services," the final rule expands this to bring "completeness, adequacy and quality of the services furnished in the hospital" within the purview of the review agency. The requirement of a review of random sample of discharges was changed to indicate that this review will take place at least every three months as opposed to every six months.

These review processes were installed because the problems that could arise under the new economic incentives include unnecessary or marginal admissions and early discharge followed by readmission—a practice that would cause payment twice for the same case. Hospital personnel could also fudge diagnoses in order to move patients into higher paying DRG categories, a phenomenon known as "DRG creep." The Health Care Financing Administration has begun admission pattern monitoring so that it will have base-

line data from which to judge suspicious changes in admission patterns.

Another area related to quality of care that may be affected by the DRG system is nursing service in hospitals. Nurses may become either heroes or casualties in the battle for reimbursement.

Nursing as a Target

Currently, expenditures for hospital and physician services are two of the principal targets of cost containment efforts. Nursing could become a third target separate from the overall hospital component. A New Jersey study showed that, on the average, 35% of a hospital's budget is concentrated in the department of nursing and 55% of the manpower budget, exclusive of the hospital-based physician costs, is devoted to nursing service personnel.

The Federal Government could, for example, pay for certain services only if they are rendered by the least costly and least trained personnel. Even more worrisome would be possible governmental decisions to pay only for certain staffing ratios. These could preclude the possibility of an all registered nurse staff or require that hospitals minimize nursing unit costs by hiring larger proportions of licensed vocational nurses, aides and orderlies. Such decisions could result in inadequate, unsafe or poor quality care.

Some have described a new role of nursing administrators and head nurses as that of a "foreman" monitoring use of limited hospital resources. Nursing directors would be able to see by cost center the consumption of resources. With computerized data they will analyze the consumption of supplies and nursing staffing patterns, which will be reported in dollars and cents, rather than in staffing ratios. The role of nursing manager could become one of an executive in charge of care in a product line such as obstetrics, orthopedics or the like.

Effect on Technology

Technological advances have allowed for improvements in the quality of medical care. DRG incentives may be expected to affect technology use in several ways: (1) overall, the number and intensity of ancillary procedures can be expected to decrease; (2) the incentive to reduce costs will encourage concentration of capital-intensive technologies in fewer institutions; (3) a change in technology product mix is likely to result from downward pressure on the price and quantity of supplies and, if capital is included in the DRG rate, capital equipment. Hospitals will examine more closely whether the benefits of implementing a particular technology outweigh the costs. How much does each piece of equipment contribute to the bottom line? Should it be renewed or is it drawing dollars out of the system?

Hospital Administrators Embrace Profit Concepts

As one can see, the DRGs have brought the imperatives of the corporate board room into the hospital environment. Corporate business planning, cost accounting, product line management—words that not too long ago would have no place in hospital corridors—are now becoming commonplace. Now, cost accounting, labor productivity and strategic planning have become important aspects of health care. Now the "health center" is becoming the "profit center." The commercialization of medicine is upon us.

Operating in an environment of cost constraint, hospitals will be compelled to give microscopic examination to every aspect of their operations in which their actual costs exceed the applicable fee paid by Medicare. Hospitals will and are developing case management information systems which will integrate clinical, financial and productivity data. These computerized data will give much information, such as

- How much of the hospital's resources—laboratory, radiology, respiratory therapy—is being used for each DRG or DRG grouping? How does an individual physician compare with other physicians? How does the cost of these services compare to the standard cost per DRG? Which DRGs require the greatest use of resources?

- The data will give the hospital cost and income information for each clinical program such as renal dialysis, open heart surgery, etc. The hospitals will look at these programs just as a business looks at separate divisions within a corporation. How much income per DRG is received from patients who use the service? Is the service profitable? Is it worth being expanded? Should it perhaps be eliminated?

- Development of financial profiles for the clinical programs means looking at clinical programs in terms of the kinds of DRG patients who use the programs, the volume of business and the cost of running the programs. The data tell the hospitals the amount of revenue and expenses generated by each physician in each clinical program.

- The information can show how much of the market share the hospital is capturing for each DRG. Does the market share justify the continuation of the program? Should the hospital expand its market share by aggressive promotion and selection of physicians who bring these DRGs to the hospital?

These DRG data reports will help hospitals make decisions about facilities, equipment and supplies. Hospitals will most likely base their construction and remodeling plans on the perceived availability of patient DRGs. As the trend to outpatient services grows, hospital management will put its money into outpatient facilities. As the hospital's patient population grows older, it will have to respond by providing beds in long-term care units, affiliated nursing homes, hospice programs and home care settings. In these ways DRGs will have a direct effect on the hospital's physical planning.

As you can see, DRGs have implications for the future of hospitals and physicians far beyond merely placing patients in certain categories and determining

how much hospitals will be reimbursed for them. The hospital will be no different than any large corporation which utilizes statistical data for strategic planning.

Inevitable Impact on Practicing Physicians

Using the management information systems, physician practices will be assessed. The monitoring system, or so-called physician profiles, will evaluate the patterns of admission and utilization and identify practice and admission patterns that are economically "harmful" to the hospital. There will be discussions about the physician's performance (defined as service ordering behavior) related to the DRG rates. But, we physicians must know not only how our service ordering behavior compares with the DRG rates but what are the actual costs that are associated with the services that are rendered. At this time, most hospitals do not know what their true costs are.

The administrators, armed with the clinical and cost data generated by their hospital information systems, can then press physicians with high-cost practice patterns to cut back in such areas as patient length of stay or use of ancillary services. Hospitals can also attempt to interest physicians and change their behavior in cost containment by an attractive structuring of financial incentives. A hospital may find it effective to pay attending doctors year-end bonuses that are tied to their ability to make certain administratively set financial targets. There have been several proposals to structure medical departments as profit centers and to relate physician remuneration to the financial performance of their particular service. These types of incentives are a means of achieving de facto incorporation of the attending physician into the hospital's control system.

There will be attempts made not only to control physicians in their medical decision making, but to control the composition of medical staffs. Attempts may be made to use the DRG imperatives as justification for data base credentialing, by which staff privileges would be granted based not only on professional qualifications but also on cost effectiveness. A representative of the American Hospital Association has predicted that recruiting, credentialing and reappointing of physicians on hospital medical staffs will become critical factors in cost containment. DRGs will provide an increased incentive to select cost-effective physicians who know how to operate in an environment of economic restraint. Being qualified according to some may no longer be enough. Consideration may be given to whether a physician can contribute to the hospital's overall marketing plan.

Medical Staff Independence Gains Importance

All this prompts the obvious question: Can a hospital curtail or revoke staff privileges of a physician whose practices do not conform to the norms superimposed by DRGs? The answer lies within the bylaws of the organized self-governing medical staff. There is legal recognition—both in statute and case law—of the medical staff distinct from the hospital. The California Health and Safety Code, for example, requires that the medical staff be self-governing with respect to the professional work done in the hospital.

One of the essentials of medical staff self-governance is the medical staff bylaws that establish the relationship with our colleagues in the hospital and provide protection to the members of the medical staff. The medical staff bylaws stipulate the procedures and criteria for appointment to, and retention of, staff privileges. The bylaws have traditionally focused on medical and professional competence and are not likely to have provisions that in any way contemplate denying or revoking membership on the basis of economic considerations. Our bylaws must remain inviolate from attempts by hospital management to unilaterally amend medical staff bylaws in part or by adoption as a whole. The concern that the medical staff has regarding such unilateral board action is that such action may be arbitrary and self-motivated, without concerns for the rights of physicians or patients.

As one can see, this payment system will place stresses on the relationship between hospital management and physicians on the medical staff. Hospital management is confronted with *economic survival* issues. The hospital medical staff will be confronted with the *quality of care* issues. Physicians will be willing to cooperate in a true, equal partnership endeavor, but physicians will not support imposed hospital dictums that do not reflect medical staff concerns. Even the most cost-conscious physicians are going to resist limitations on the delivery system geared entirely toward reducing cost. The medical staff obviously wants to keep the hospitals open and financially sound but physicians must always be patient advocates. Traditional ethical norms dictate that a physician's primary obligation is to patients, not to others—whether they be relatives or institutions—or even the physician's own welfare. Our canons of ethics must not be destroyed by the canons of economics.

DRG Committee

The medical staff should form a DRG committee and have access to the raw data that will be generated by these case management information systems. The DRG committee activities would include review of the following:

- Monthly data on the average cost per DRG;
- Cost per DRG by physician;
- Cost per DRG by specialty area;
- High-cost DRGs to determine presence of unnecessary costs;
- Monthly length of stay statistics and physician utilization patterns by DRG.

Physician involvement is imperative in analysis of the data. Raw data do not interpret utilization patterns, only physicians can do that. The data by themselves do not differentiate costs versus charges nor establish accountability for costs. Physician involvement is

necessary for establishing clinical standards in all these areas. If a medical staff allows others to interpret, utilize and "massage" the data, they will be in danger of losing their self-governance. The medical staff will no longer be self-governing, but governed by others, with the governors having control of the computer software and data.

Physician participation and involvement in hospital decision making and policy formation is more important than ever. The successful hospital will integrate the medical staff into operational budgeting, capital budgeting and all activities of the institution. Physicians can no longer be concerned solely with issues that affect their individual practices but must involve themselves with the collective concerns of the hospital medical staff and seek ways to deal with these concerns.

Survival Possible Despite New Constraints

The winners in this marketplace environment will be those hospitals where there is the best relationship among the board, executive management and medical staff. There must be *equality* between hospital management and the medical staff. There must be *parity of information* between administration and the medical staff.

Hospital management and physicians should be willing and prepared to put their own houses in order. Physicians should not expect immunity from criticism for demonstrated overtreatment or ordering tests wholly unrelated to the quality of care. Similarly, before seeking to lay blame elsewhere, hospitals should expect to be held accountable for mismanagement and management excess. Before a hospital attributes an unfavorable cost-payment balance to physician practices, it must be prepared to open its accounting books to the staff to a greater degree than ever before.

The situation is precarious. We must not stand aside and let events control us. As Aldous Huxley said, "Experience is not what happens to you but what you do with what happens to you." Just what we do may determine the direction of our honorable profession for many years to come.

Medical Schools of the West

The University of California, San Diego, School of Medicine

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The San Diego Campus of the University of California (UCSD) grew out of the world-renowned Scripps Institution of Oceanography located in La Jolla, which has been part of the University of California system since 1912. Under the leadership of Roger Revelle, a Graduate School of Science and Engineering was established in 1960 and plans for a general campus at San Diego were adopted by the regents in 1963.

At about the same time, the state legislature was considering locations for establishing additional medical schools in response to a perceived need for more physicians in California. Aggressive lobbying by the San Diego medical and business communities coupled with demographic imperatives resulted in the regents selecting San Diego as a site for a new medical school. This was reaffirmed by the legislature in 1958. Coincidentally, the county of San Diego was planning to rebuild the county hospital and expressed strong interest in a university affiliation. Despite a major external committee report that advocated locating the school at the county hospital site, 14 miles from the main campus, in 1962 the regents approved a plan for basing the school on the campus, believing it would thrive best in the exciting scientific environment already present and growing rapidly at the La Jolla site. This plan included the development of a campus hospital and a long-range commitment to the use of the county hospital. The first dean of the new school was appointed in 1964. In 1966 an operating agreement with the county of San Diego was signed that insured the use of the new county hospital by the university, with full operating control vested in the university. The charter class of 47 medical students was admitted in fall 1968 as the school's first building was nearing completion.

During the school's formative years in the middle and late 1960s, optimism ran high for the new university and the new school. The national and state economies were booming, biomedical research for each new medical school was the order of the day and prospects for construction funds and relatively small student-faculty ratios appeared bright. In keeping with the philosophy of the developing campus, recruitment proceeded from the top down. That is, stellar physician-scientists were recruited as department chairpersons as sights were set on creating an outstanding medical school from the very beginning instead of achieving this goal gradually by evolution. To paraphrase Dr Clifford Grobstein, dean from 1967 to 1972, the stars were the target. Although not all expectations were fulfilled, we gained much more than a cautious strategy would have yielded.[1]

An unusual organizational structure that has survived to the present was chosen for the new school. The decision was made that there would be no separate basic science departments in the School of Medicine. Instead, faculty members in relevant general campus departments such as biology, chemistry and sociology are supported by the School of Medicine and participate fully in the school's curriculum and other activities. At the same time, expanded clinical departments were charged with the major responsibility for preclinical teaching and were staffed accordingly. The nine original School of Medicine departments were Community Medicine (since renamed Community and Family Medicine), Medicine, Neurosciences, Pathology, Pediatrics, Psychiatry, Reproductive Medicine, Radiology and Surgery. The Department of Anesthesiology was added in 1974 and the Department of Ophthalmology in January 1983. This complement of 11 departments contrasts with 19 to 25 at our sister medical schools in the University of California system.

A system of strong faculty governance assured ample faculty input into the curriculum. The curriculum that was developed was relatively unusual for the time, and

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has remained intact with only minor modifications. It includes cell biology and biochemistry, organ physiology and pharmacology, basic neurology, anatomy, pathology, social and behavioral sciences and introduction to clinical medicine in the first two years (Figure 1). The unusual placement of anatomy in the second year, coupled with its teaching by surgery and radiology faculty, created much distress in anatomy circles but has worked out exceedingly well. Although doubts were expressed that physiology and pharmacology could be taught in a single course, utilizing primarily clinically oriented faculty, this innovation has been successful. Traditional clerkships are offered in the third year, and the fourth year is devoted to electives (as well as a significant portion of the first two years). As part of the elective program, students select an area of concentration tailored to each student's interests and supervised by a small faculty group. The concentration area culminates in a written thesis or equivalent scholarly accomplishments such as films, books and new courses.

To enhance student-faculty interaction, reduce stress on students and inculcate a spirit of self-learning as opposed to cramming for examinations, a pass-fail system of grading augmented with narrative performance evaluations was instituted for each course. Strong student sentiment against ranking, honors and the development of academic honor societies such as Alpha Omega Alpha persists.

The 1970s—A Decade of Growth

The 1970s were a time of rapid growth of the school. By the end of the decade the faculty included more than 400 full-time faculty members and 1,300 voluntary clinical faculty members. Teaching and research facilities were constructed on the La Jolla campus and at the UCSD Medical Center—the renamed San Diego County Hospital. Extensive physical improvements were carried out at the medical center such as converting large wards to semiprivate and private rooms, major expansions of all diagnostic capabilities and construction of an outpatient wing. In addition, several tertiary referral services were developed, including a trauma center, burn unit and neonatal intensive care unit. Services were also developed to cover the full gamut of primary and secondary patient care needs. In 1972 the new 600-bed Veterans Administration Hospital opened adjacent to the School of Medicine facilities on land provided by UCSD on the La Jolla campus (Figure 2).

Unlike most large West Coast communities, San Diego had a dearth of house-staff training programs

Figure 1.—The Basic Sciences Building, UCSD School of Medicine.

when the school began its operations. A broad spectrum of programs existed at Balboa Naval Hospital and there were several small programs at Mercy Hospital. House-staff training at the new Veterans Administration Hospital was fully integrated into University Hospital training programs. The school developed major affiliations for training of its house staff and medical students at Mercy Hospital, Balboa Naval Hospital and Children's Hospital and Health Center. Important but less extensive affiliations were effected with Kaiser Permanente Hospital, Sharp Memorial Hospital, Green Hospital of Scripps Clinic, City of Hope (Los Angeles), Kern Medical Center (Bakersfield, California) and Tuba City (Arizona) Indian Hospital. A variety of community clinics and physician preceptors are also integral to clinical training activities. In addition to pursuing their studies in San Diego, most students elect to gain some clinical experience in other medical centers both here and abroad. A sizable number pursue special projects in developing countries.

Affiliations also extend to research activities. Fruitful interactions were established with the Salk Institute for Biological Studies and the Scripps Clinic and Research Foundation, both of which border on the campus, with the San Diego Zoo and with Sea World. Research at UCSD has flourished and the School of Medicine consistently ranks among the top four or five medical schools in the nation in terms of research funding per full-time faculty member. A number of National Institutes of Health-supported specialized centers of research and a clinical research center were established.

Simultaneously, the school responded to the expressed social concerns of the 1970s. Successful minority recruitment and student retention programs were instituted; a major community clinic was developed in San Ysidro to serve a large Hispanic population. This clinic was later turned over to the community. Assistance was also given to the development of other community clinics.

In the early 1970s, state and national priorities were focused on the apparent need for greatly expanding the output of physicians. Later in the decade, this concern was redirected toward a perceived specialty maldistribution of physicians. In response to the first, the school expanded its planned steady-state class size from 96 to 128 students. In response to the second, a Family Medicine Program was developed together with general medicine and general pediatrics residency tracks. A Nurse Practitioner/Nurse Midwifery Program was also launched successfully. The County Paramedic Training Program was initiated by the school, and is still carried out under its auspices.

The success of the UCSD medical students is perhaps unparalleled in the development of new medical schools. Starting with the charter class, the students have consistently placed in the upper 10th percentile nationally on Part I of the National Boards. Toward the end of the decade, performance on part II achieved

Figure 2.—Anatomy class meets outdoors. The Veterans Administration Hospital is in the background.

and has stayed at the same levels. The applicant pool quickly reached and remains steady at the 4,000+ level. Students and faculty interview about 700 "finalists" annually. This effort contributes significantly to the matriculation of students who are academically qualified to meet the stringent demands of the curriculum, who display the qualities necessary for effective doctor-patient interaction and who have a commitment to the professional and social concerns that the profession must address.

In 1979 the school received the first ten-year accreditation granted by the Liaison Committee on Medical Education.

The Realities of the 1980s

In the 1980s, medical schools are again adjusting to changing social imperatives. Overproduction of physicians is now a major concern. The health sciences are no longer the darlings of state and federal legislatures. Economic slowdown has forced a reevaluation of the priorities for health professions education, health care and—to a certain extent—health-related research. Sources of capital funding needed for plant renovation and expansion to meet the changing requirements of health care and medical research are increasingly difficult to identify. Major changes occurring in health care financing are likely to work to the disadvantage of academic health centers that offer the most expensive tertiary level care and have major commitments to education. These changes are also affecting the academic medical centers' relationships with their affiliated hospitals.

The UCSD School of Medicine is not exempt from these perturbations. The entering class size has been reduced from 128 to 122 students. A debate is raging about the role, program mix and relative level of house-staff training under the auspices of the academic medical center. Inadequate attention has been paid in these debates to the role of the house staff in providing patient care and in the education of undergraduate medical students; to the interrelationships among the house-staff training programs, and to the need for high-quality graduate medical education opportunities for California graduates (the number of first-year house-staff positions nationally continues to decline in the face of a still rising output of medical school graduates). UCSD now is responsible for the training of 430 house officers including the integrated programs at the Veterans Administration Hospital and at a number of community hospitals.

Despite cutbacks, our commitment to diversified educational and training opportunities remains intact. In 1982-1983, the medical student body numbered 504, of which 26% were women and 27% ethnic minority students. Over the years, changes in the curriculum have included the addition of a requirement for 12 weeks of direct patient care experiences in the fourth year; four of these weeks must be in an outpatient setting. The concentration area requirements have been modified somewhat and are now described as an independent study project that must culminate in a paper or other tangible expression of scholarly accomplishment. After lengthy debate, the pass-fail system may be modified to include honors and high-pass options. The school has primary responsibility for 115 students in graduate programs in pharmacology-physiology, neurosciences and bioengineering, more than 200 research fellows and the nurse practitioner program. In addition, our faculty participates in general campus graduate and undergraduate programs in biology, chemistry and psychology. The medical center accommodates nursing and allied health students in 19 programs associated with 16 other educational institutions. Potentially, the competitive environment could affect our ability to provide clinical training for these students. We also serve as a clinical training site for 16 University of California, San Francisco, pharmacy students. Our formal continuing education programs for physicians are now reaching 6,000 participants annually.

Figure 3.—Gildred Cancer Facility with UCSD Medical Center in the background.

We continue to hold our own in biomedical research. UCSD is the only one of the 49 medical schools founded since World War II to rank among the top 25 medical schools in private and federal support of research. Our Cancer Center, which has functioned as a regental-approved organized research unit since 1979, continues to expand its basic science base while offering ever-increasing opportunities for participation in clinical trials by community oncologists. The Gildred Cancer Facility (Figure 3), which houses a major portion of the Cancer Center activities including the oncology clinic, was dedicated on April 15, 1983. It was made possible by the success of our first local fund-raising effort and a National Cancer Institute grant. In March 1983 the regents approved the establishment of

the Institute for Research on Aging. Aging is an area in which we expect major growth in research and creative expansion in teaching and patient care.

We anticipate that the UCSD Medical Center, University Hospital, which was purchased from San Diego County in 1981, will continue to respond imaginatively to the changes in health care financing by both the public and private health sectors and will continue to grow in selected areas. Services as diverse as the Life Flight Helicopter Service, a Medical Center and community-based adolescent medicine program, an Indonesian health education program and a nuclear magnetic resonance facility have recently been or are about to be added.

A small internal medicine clinic is operating near the school on the La Jolla campus. Studies are under way to determine the feasibility of developing a campus hospital or other health care facilities (or both), an indication of our optimism for the future. A campus hospital would address needs that have been expressed since the establishment of the school. These include substantially improving opportunities for clinical research; providing a significantly improved patient mix for teaching, and enhancing private practice opportunities for the faculty. Even if a campus hospital eventually comes into being, UCSD Medical Center in the Hillcrest area will continue as an integral part of the school's programs.

Conclusion

Dr Clifford Grobstein's statement in 1972 "that the [medical school] plan underwent metamorphosis rather than disruption is a testimony to its original soundness" can be reiterated 12 years later.[1] The historic challenge to medical schools remains: to maintain high-quality training programs, incorporating in their curricula new knowledge while responding to major societal and environmental changes. In a climate of continuous public pressure for quick solutions in medical education and medical care, and in the face of new threats to the stability of clinical programs, responding to the challenges of the future will require more effort and imagination than ever before. UCSD School of Medicine anticipates meeting this challenge, working with the San Diego community, the local medical profession and the university toward improving its own programs while contributing positively to the formulation of public policy as it affects medical education.

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Commentary

Commentary From Coeur d'Alene: 1984—A Year of Prophecy?

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

We are now in the year 1984, the fateful year of Orwellian prophecy. We could wish that somehow each of us might be granted the ability to prepare for the future by looking into the past, like the mythical god Janus, who with his two faces could look both backward and forward.

Were we to attempt forecasting the future of medicine, let us hope that we would do it with optimism, and less of the pessimism of a George Orwell.

Every student of the history of medicine must come to this realization: The practice of medicine is dynamic, ever changing with the swings of the pendulum of public opinion, just as the physician's image undergoes wide swings in popularity.

Only 150 years ago, during the Jacksonian era, the medical profession was held in low esteem, and medical licensure carried with it little honor. Indeed, the image of physicians had sunk so low that several state legislatures wanted to do away with medical licensure altogether.

Medicaments, as such, were to be avoided; home remedies abounded. Natural forces were relied upon to bring about healing. Illness was considered punishment for sin, and health came from God, not from doctors.

There was no pride attached to the name "doctor of medicine," and even then the authority of physicians was being questioned by an increasingly aggressive nursing profession.

With the passing years a gradual change took place. During the first five or six decades of this 20th century the status of the medical profession rose to new heights. The "good doctor" who sat by the bedside, who brought health and babies in his black bag, was again deified by his loyal patients. Once more the popularity polls placed physicians at the top, right along with members of the clergy.

Today there are indications that medical history is repeating itself, that the pendulum is again on the downswing.

The legislature of a large, progressive bellwether state we often look to for leadership has questioned the need for medical licensure. "Natural" foods, medicines and herbs are extolled. Faddists and quacks have subverted the fine qualities of holistic medicine. *PDRs* are sold in book stores, ostensibly to enable patients to question prescriptions physicians have given them. Advice from talk show hosts and lay magazines often outweighs the doctors' opinions.

Paraprofessionals or, as they prefer to be called, allied health care professionals are bringing pressure to be given medical staff privileges, with the right to admit and treat patients in hospital. The Joint Commission on the Accreditation of Hospitals and the American Medical Association are on the horns of a dilemma, squeezed between the urgings of medical staffs and the fears of restraint of trade legislation.

An intensive care unit nurse in Harbor City, California, refuted the order of two respected physicians, and she subsequently brought a lawsuit against them. And in a recent popularity poll, physicians dropped to a lowly third place, well behind the clergy and pharmacists.

All this comes as a blow to the pride of this physician who has worn out three "black bags." Where have we gone wrong? What can we do about it?

Troubled by these same problems, the Ohio State Medical Association (OSMA) wisely went to its member physicians, setting up discussion panels throughout the state.[1] There was considerable heat and a modicum of light developed by these panel discussions.

Third-party payors, government intrusion, prepayment medicine—these were blamed for putting the fee-for-service type of practice into jeopardy. In general, their discussions reflected a sense of despair.

Patient "education" was deplored as inadequate and superficial. They called for the medical profession to "get into the act," and at the same time begin to "blow your own horn." After all, they said the Latin word for "doctor" translates "teacher."

The increase in liability suits was viewed as a result of, rather than a cause of, the diminished physician

(Fox ERW: Commentary from Coeur d'Alene: 1984—A year of prophecy? [Commentary]. West J Med 1984 Aug; 141:261-263)

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image. In yesteryear no one would ever think of suing the "good doctor."

The institutionalization of medicine, snug in the womb of the hospital, together with the snaring by emergency rooms of the patients who previously would have gone to a doctor's office, have served to detract from the image of private physicians, especially that of family physicians.

Further, the OSMA panel members concluded that advanced technology must also share some of the blame for the lessened physician stature. Our new sophisticated gadgetry has brought with it the battalions of allied health care professionals needed to keep the machines running. The young respiratory technician with a stethoscope draped around his neck gets a glow out of being addressed as "Doctor" by a patient on the ward. How are these patients to know who is a "real" doctor?

In health care, as in home repairs, everyone is now being urged to "do it yourself." Technology has given our patients the ability to check their own blood pressure and blood glucose values, and there now are pregnancy testing kits for home use. Why then consult a doctor or pay for an office call?

The OSMA panelists did arrive at a consensus: Individual physicians' organizations must try harder to influence legislators and the public. The value of political action committee activities was recognized, but there was a fear that too often we contributed our dollars and let it go at that.

In that same context, James L. Breen, in delivering his presidential address to the American College of Obstetricians and Gynecologists,[2] reminded us that 31 physicians took part in the First Continental Congress and 6 physicians were signers of the Declaration of Independence.

One additional and terribly important factor in this downgrading of the physician's image must be mentioned: That is the trend toward specialization and subspecialization, to the detriment of the generalist. An editorial in *JAMA*[3] deplores the increasing influences of specialists and subspecialists, particularly in hospital practice. This is by no means a baseless fear. The executive committee of our community hospital staff, under a plan of "departmentalization," will be made up of nine specialists and subspecialists, and *one* generalist.

The administrator of our hospital proudly announced to the local press (*The Spokesman-Review*, Spokane, Wash, Jan 8, 1984) that

> The hospital opened in 1966 with a staff consisting almost entirely of general practitioners, with one or two surgeons. Half of the present staff has arrived since 1977, and the list now includes specialists and subspecialists in neurology, rheumatology, gastroenterology, among others.

Robert G. Petersdorf, dean of the University of California, San Diego, School of Medicine, speaking at the Washington State Medical Association's annual meeting,[4] contended that we are entering a period of "future shock" as students are lured away from general practice by the glamour of the subspecialties.

In an article, "American Doctors—A Profession in Trouble," *US News and World Report* editor Britt looked at the many forces that threaten "medicine's rugged individualism of the past" (*US News and World Report*, October 17, 1977). She bemoaned the fact that "Today only one-seventh of this country's physicians are in primary care—although 90% of the problems that send patients to the doctor do not require specialty training."

All will agree that the downswing in the image of primary physicians has resulted in a great part from the upswing in medical technology. The specialists control the diagnostic and therapeutic machinery, and therein lies the glamour.

However, this addiction to technology has produced what Dr Ralph Cramshaw[5] calls "a new, dangerous iatrogenic disease, the syndrome of the technical fix." Cramshaw protests, "Physicians appear blind to how the machine intervenes between the patient and the doctor." He calls for a rethinking of the physician-machine relationship.

There may already be forces at work in this year of prophecy, forces that will temper the winds of technology, saving us from being captives of our own sophisticated machinery.

One force, and a potent one, is the economy. For more than a decade we, the physicians, the hospitals and our patients, have been living high at the medical care banquet table. First class care was promised to one and all. This included unlimited CT scans, sonograms, arterial gas determinations, fetal monitoring and laboratory tests ad infinitum. Not to worry about costs —our patients are "covered" by third-party payors, Medicare and a benevolent Big Brother in Washington.

Yet Big Brother has now, belatedly, awakened to the fact that the banquet must come to an end. The first class medical meals must be pared down to tourist class. And this is to be accomplished through the use of Diagnosis Related Groups (DRGs).

DRGs are hailed by some and damned by others. Hospital administrators are suddenly confronted with a prospect of red ink on the balance sheet after a long and euphoric period of black-ink prosperity. Nursing staffs are being cut, formularies are being narrowed (first-generation cephalosporins will do), and we staff members are being urged, even pressured, to limit our ordering of the batteries of exotic tests that only yesterday seemed so necessary. We are learning, also, that we had best discharge our patients promptly, within the DRG time limitation.

Now then who among us, the primary physician or the superspecialist, has most often been guilty of ordering the batteries of "unnecessary" tests, or of prolonging the hospital stay for just one more diagnostic dessert?

Although the DRG system of payment so far applies only to Medicare patients, it is conceded that if the plan proves cost-effective it will be extended to a full

range of patient care reimbursement. This may be considered by some as another third-party intrusion, and yet it could bring with it some benefits not originally perceived by the designers of the plan.

As Dr Malcolm Watts has pointed out in an editorial in this journal,[6] "In recent years a strong focus on medical science has somewhat overshadowed the art . . . it would seem that DRGs will add yet another dimension to this art of a practicing physician . . . in both the patient and the public interest."

There are still other potent facts pointing us away from the impersonal, mechanized, specialized medical care. In several subtle ways our patients are pleading for a return to the "rugged individualism" of medical practice. Home health care, hospice, birthing rooms, free-standing surgicenters, drop-in "urgency centers," all tell us that the public yearns for a return to the "good doctor" who is both friend and physician.

One present-day oracle, John Naisbitt, the author of *Megatrends,*[7] writes with optimism that George Orwell did not possess. Naisbitt believes that we have been living in "a time of parenthesis, a time between eras." He believes that in the era ahead of us, whether in business, industry or medicine, "if you specialize too much, you may become obsolete. Now we need more generalists who are constantly remodeling their skills." He, too, is calling for a return to the art of medicine.

Private practice is not dead, but alive and well. The primary physician, even the much maligned solo practitioner, would seem to be standing on the threshold of a new era, looking forward to a brightened physician image, as once again the pendulum swings.

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In Memoriam

Correction

In the July 1984 issue, page 132, it was erroneously reported that Lawrence B. Williams, MD, of Santa Barbara, California, had died. The journal regrets the error and apologizes to Dr Williams.

California Medical Association

ABRAMS, LOUIS, Los Angeles. Died October 10, 1983, aged 62. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1950. Licensed in California in 1950. MD degree from California College of Medicine, 1962. Dr Abrams was a member of the Los Angeles County Medical Association.

FRANCIS, REGINALD K., Inglewood. Died December 11, 1983, in Inglewood of metastatic malignant melanoma, aged 85. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1922. Licensed in California in 1923. Dr Francis was a retired member of the Los Angeles County Medical Association.

GOLDFISHER, JOSEPH S., Los Angeles. Died March 2, 1984, aged 61. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1953. Licensed in California in 1954. MD degree from California College of Medicine, 1962. Dr Goldfisher was a member of the Los Angeles County Medical Association.

HALVERSON, GLEN R., Riverside. Died September 14, 1983, aged 83. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1934. Dr Halverson was an associate member of the Riverside County Medical Association.

HERZEN, ALEXANDER V., Los Angeles. Died November 1, 1983, aged 83. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1947. Licensed in California in 1947. MD degree from California College of Medicine, 1962. Dr Herzen was a member of the Los Angeles County Medical Association.

LENARTZ, BRUCE J., Escondido. Died April 5, 1984, of injuries received in an automobile accident, aged 46. Graduate of the University of Wisconsin Medical School, Madison, 1963. Licensed in California in 1964. Dr Lenartz was a member of the San Diego County Medical Society.

MORRIS, WILLIAM M., Pomona. Died September 7, 1983, aged 68. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in California in 1959. Dr Morris was a member of the Los Angeles County Medical Association.

MULFINGER, CARL L., Los Angeles. Died September 20, 1983, aged 89. Graduate of the University of Illinois College of Medicine, Chicago, 1923. Licensed in California in 1923. Dr Mulfinger was a retired member of the Los Angeles County Medical Association.

RAHN, PAUL C., Calistoga. Died March 4, 1984, aged 77. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1936. Licensed in California in 1936. Dr Rahn was a retired member of the Alameda-Contra Costa Medical Association.

RUIZ, JUANA, Glendora. Died September 20, 1983, aged 59. Graduate of the University of Southern California School of Medicine, Los Angeles, 1950. Licensed in California in 1950. Dr Ruiz was a member of the Los Angeles County Medical Association.

SHORE, CHARLES, Los Angeles. Died October 14, 1983, aged 60. Graduate of University of Buffalo School of Medicine, 1948. Licensed in California in 1950. Dr Shore was a member of the Los Angeles County Medical Association.

SIBBETT, WILLIAM ALBERT, Los Angeles. Died January 19, 1984, aged 64. Graduate of the Medical College of Georgia, Augusta, 1955. Licensed in California in 1956. Dr Sibbett was a member of the Los Angeles County Medical Association.

TIDD, CHARLES W., Los Angeles. Died November 7, 1983, aged 80. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1933. Dr Tidd was a retired member of the Los Angeles County Medical Association.

TRAGERMAN, L. JOHN, Los Angeles. Died October 3, 1983, aged 75. Graduate of Rush Medical College, Chicago, 1933. Licensed in California in 1933. Dr Tragerman was a retired member of the Los Angeles County Medical Association.

WELLS, THOMAS J., El Cajon. Died October 2, 1983, aged 62. Graduate of Creighton University School of Medicine, Omaha, 1946. Licensed in California in 1946. Dr Wells was a member of the San Diego County Medical Society.

WILDHABER, JOSEPH B., Arcadia. Died January 26, 1984, aged 64. Graduate of the University of Nebraska College of Medicine, Omaha, 1946. Licensed in California in 1955. Dr Wildhaber was a member of the Los Angeles County Medical Association.

New Mexico Medical Society

CLEVENGER, MARSHALL L., Albuquerque. Died May 14, 1984, in Albuquerque, aged 63. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1950. Licensed in New Mexico in 1958. Dr Clevenger was an emeritus member of the Albuquerque & Bernalillo County Medical Association.

SCHULTZ, CLEON L., Roswell. Died in May 1984 in Roswell, aged 56. Graduate of the University of Wisconsin Medical School, Madison, 1959. Licensed in New Mexico in 1964. Dr Schultz was an emeritus member of the Chaves County Medical Society.

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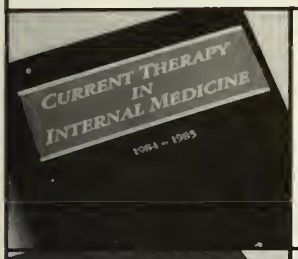

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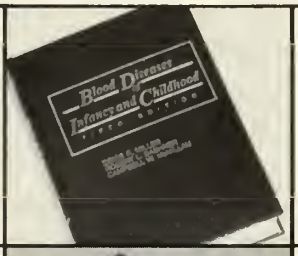

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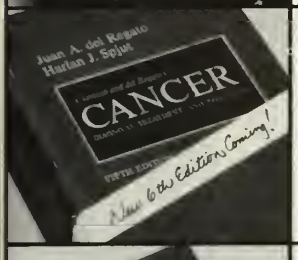

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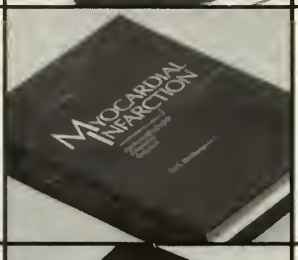

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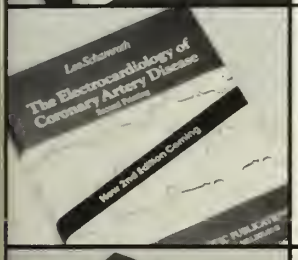

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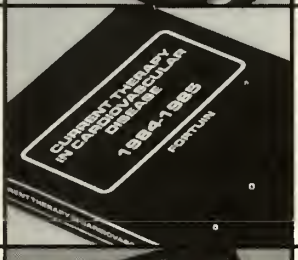

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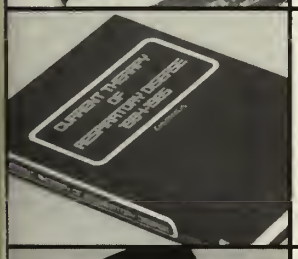

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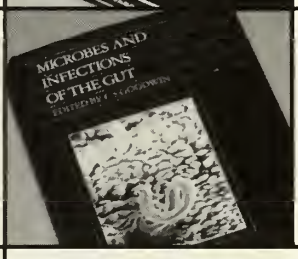

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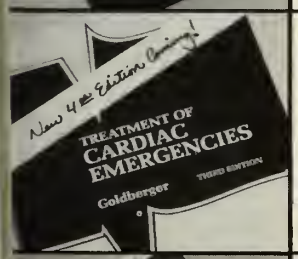

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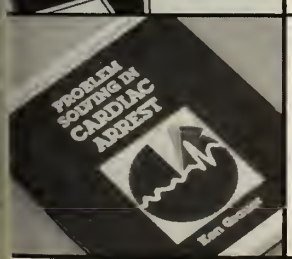

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FAMILY PRACTICE	ABCs of Aging
EMERGENCY MEDICINE	Inside/Outside the ER
ANESTHESIOLOGY	Computers in Medicine
ALLERGY & IMMUNOLOGY	Update for the Primary Care Physician
PSYCHIATRY	Short-Term Dynamic Psychotherapy Theory and Practice
PEDIATRICS	Selected Topics in Pediatrics

Guest Speakers will include

JOHN D. ABRUMS, MD, FACP
President, American Society of Internal Medicine
Albuquerque, NM

HABIB DAVANLOO, MD
Professor of Psychiatry
McGill University
Montreal, Canada

HARRY WONG, MD
Chairman, Committee on Ambulatory Care
American Society of Anesthesiologists
Salt Lake City, UT

ROBERT BURNETTE, MD
President and Founder of LifeGuard
Santa Clara, CA

A complete copy of the scientific program is available from the Washington State Medical Association, 2033 Sixth Avenue, #900, Seattle, WA 98121, (206) 623-4801

Socio-Economic Session

Physician-author STANLEY M. WOHL, MD, is scheduled to speak to WSMA members from 11:00 a.m. to noon on Friday, September 14, 1984. Wohl, author of *The Medical Industrial Complex,* will offer insights on the growing impact of corporate maneuvering on the practice of medicine and recommendations for physician response.

If you would like additional information regarding the 95th WSMA Annual Meeting, detach and return the completed form below:

Return to:
Washington State Medical Association
2033 Sixth Avenue, #900
Seattle, WA 98121

Please send me more detailed information on the 1984 Washington State Medical Association Annual Meeting

NAME _____

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(Continued from Page 180

Fresno. Saturday. Contact: Sharon Balestra (209) 225-6100 Ext. 562 or 207.

November 14—**Rheumatology—X-Ray of the Joints.** LLU. Wednesday.

November 16-18—**Pulmonary Medicine and Office Spirometry for P.C. Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday.

OBSTETRICS AND GYNECOLOGY

August 9-11—**Basic and Advanced Colposcopy.** American College of Obstetrics and Gynecology at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: ACOG Reg., Ste. 300 E, 600 Maryland Ave., SW, Washington, DC 20024.

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

August 29-31—**Biennial Meeting and Conference of The Marce Society** at Claremont Resort, Oakland. Wednesday-Friday. Contact: James A. Hamilton, MD, 490 Post St., Ste 1515, San Francisco, CA 94102.

September 12—**OB/GYN—Menstrual Disorders.** LLU. Wednesday.

September 28-29—**Outpatient Gynecology in the 1980's Progress and Expectations.** Center for Health Education at Long Beach. Friday-Saturday. 10 hrs. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 6—**Clinical Ultrasound—OB/GYN Update.** Sacramento Radiology Research and Education Foundation and the Northern California Radiology Society. Saturday. $75. Contact: J. P. McGahan, MD, Program Director, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 7-9—**The Neural and Metabolic Bases of Feeding.** See Pediatrics, October 7-9.

October 22-27—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** UCI. Monday-Saturday.

OPHTHALMOLOGY

August 25—**Neodymium: YAG Laser Workshop.** JSEI. Saturday.

October 10—**Ophthalmology-Therapeutic Decision re: Glaucoma, Retinopathy and Cataracts.** LLU. Wednesday.

October 11-13—**Cosmetic Blepharoplasty Workshop.** JSEI. Thursday-Saturday.

October 20—**Update for Nonophthalmologists: Ocular Diseases of Aging.** JSEI. Saturday.

November 30-December 1—**Phacoemulsification, Extracapsular Cataract Surgery & Intraocular Lenses.** Jules Stein Eye Institute at Los Angeles. Friday-Saturday.

PEDIATRICS

October 3-4—**41st Annual Brenneman Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Red Lion Motor Inn, Sacramento. Sunday-Tuesday.

October 20-27—**9th Annual Pediatrics for the Practitioner.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

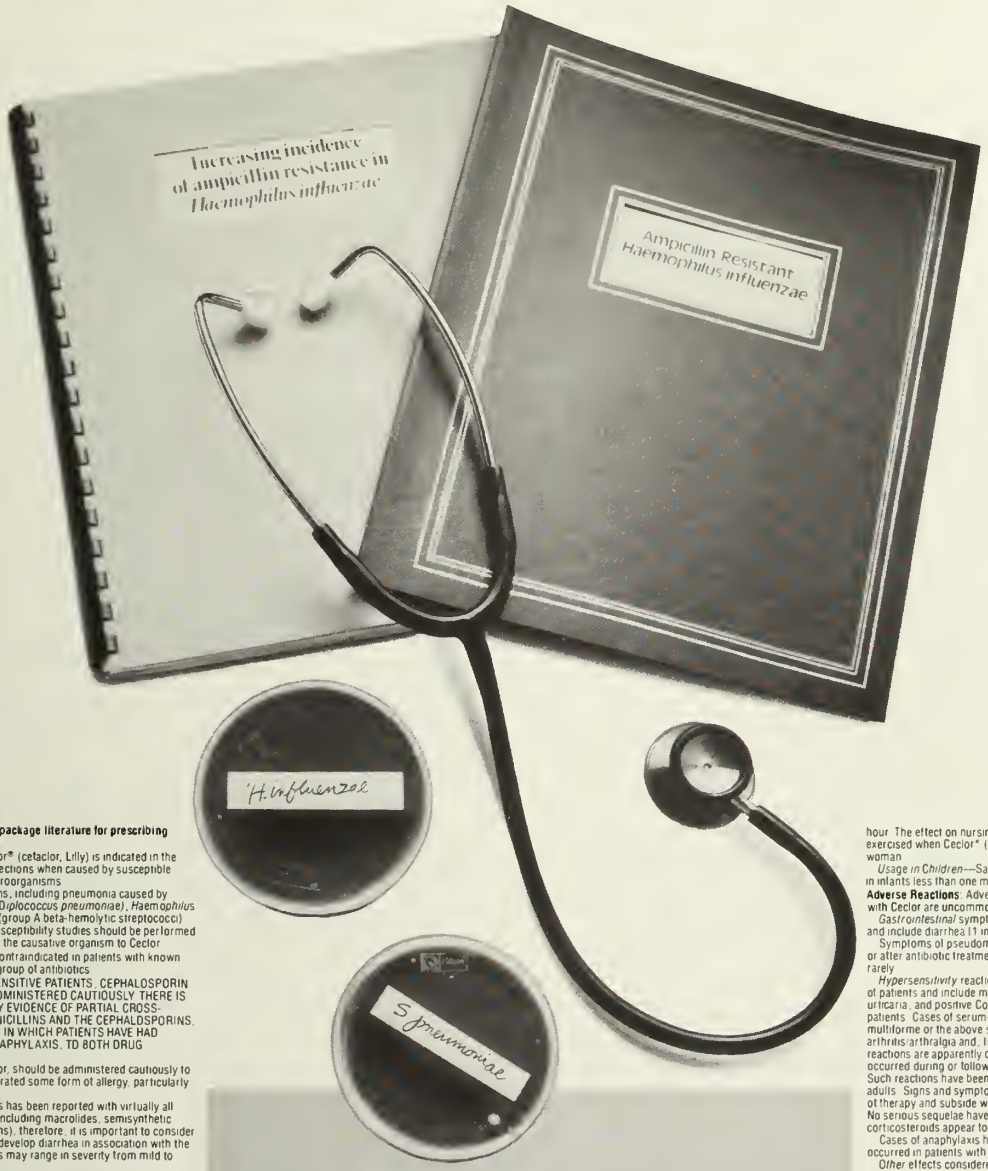
October 26-27—**Adolescents Inside and Out.** Children's Hospital Medical Center of Northern California and California Chapter 1 of the American Academy of Pediatrics at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes-Dodd, Medical Staff Office, Children's Hospital Medical Center, 51st and Grove St., Oakland 94609. (415) 428-3334.

November 10—**Physiologic Review of the Fetus and Newborn.** UCSD at Bahia Hotel, San Diego. Thursday-Saturday.

November 16-19—**Clinical Pediatrics.** California Chapters 1, 2 & 3 American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

(Continued on Page 272)

An added complication... in the treatment of bacterial bronchitis*


Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H. influenzae
S. pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor
Pulvules®, 250 and 500 mg

Brief Summary: Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor* (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis, occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

* Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., 8:91, 1975.
2. Antimicrob. Agents Chemother., 11:470, 1977.
3. Antimicrob. Agents Chemother., 13:584, 1978.
4. Antimicrob. Agents Chemother., 12:490, 1977.
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978.
6. Antimicrob. Agents Chemother., 13:861, 1978.
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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Carolina, Puerto Rico 00630

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THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

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(Continued from Page 268)

PSYCHIATRY

August 18-23—**Responsibility Issues in Mental Health.** Southern California Psychiatric Institute at Mauna Kea Beach Hotel, Kauela, HI. Saturday-Thursday. 15 hrs. Contact: Gail Waldron, MD, Program Dir., SCPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

August 22-24—**Sexually Traumatized Adults, Children and Adolescents.** Mental Research Institute, Palo Alto. Wednesday-Friday. 9 hrs. $90. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 25—**Case Studies in Brief Interactional Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $70. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

November 9-11—**30th Annual Group Therapy Symposium.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

RADIOLOGY

August 20-24—**Radiology of the Abdomen.** UCSD at San Diego and Anaheim. Monday-Friday. 27 hrs. $395.

August 27-29—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Foundation and Northern California Radiological Society at Napa Valley. Monday-Wednesday. 18 hrs. $325. Contact: Michael H. Reid, MD, Program Dir., SRREF, PO Box 19184, Sacramento 95819.

September 6-9—**Physics of Diagnostic Radiology.** UCD. Thursday-Sunday. Contact: UCD (916) 752-0328.

September 8-9—**Head and Neck Radiology: Advanced Techniques in Diagnostic Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Saturday-Sunday. 12 hrs. $250. Contact: UCSF (415) 666-5731.

September 10—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Monday. 30.5 hrs. $400. Contact: UCSF (415) 666-5731.

September 15—**Radiotherapy and Surgery Symposium "Where Do We Stand With the Management of Localized Breast Cancer?"** Kaiser Permanente at The Biltmore Hotel, Los Angeles. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 17-20—**American College of Radiology Meeting** at Century Plaza Hotel, Los Angeles. Monday-Thursday. Contact: ACR, 20 N. Wacker Dr., Chicago 60606. (312) 236-4963.

October 13—**11th Annual Radiology Symposium.** Kaiser Permanente Southern California Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 13-21—**9th Annual International Body Imaging Conference.** West Park Hospital at Royal Lahaina Hotel, Maui. One week. 28 hrs. $425. Contact: Conference Sec., 9th Annual Body Imaging Conf., Dept. of Radiology, West Park Hospital, 22141 Roscoe Blvd., Canoga Park 91304. (818) 340-0580, ext. 280.

October 19-21—**Duplex Scanning.** Institute for Medical Studies at Holiday Inn Fisherman's Wharf, San Francisco. Friday-Sunday. Contact: Kim Stroich, IMS, 30131 Town Center Drive, Ste. 215, Laguna Niguel 92677. (714) 832-2650 or 495-4499.

October 22-26—**9th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Monday-Friday.

November 5-9—**Diagnostic Radiology Seminar.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday.

SPORTS MEDICINE

October 2-6—**1st Annual Endurance Sports Medicine Symposium.** American Medical Joggers Association at King Kamehameha Hotel, Kona, Hawaii. Tuesday-Saturday. Contact: Ferdy Massimino, Dept. of Emergency Medicine, 2312 Haverhill Dr., Benicia 94510. (707) 745-2954.

November 9-11—**Sports Medicine and Outpatient Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Friday-Sunday. Contact: Jackie Shiller, CMEA. PO Box 84296, San Diego 92138. (619) 223-2997.

SURGERY

August 22-24—**Ambulatory Surgery and Hysteroscopy.** See Emergency Medicine, August 22-24.

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 17-21—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

September 20-22—**Microsurgery: An Introduction to Microtechnique for Small Artery and Nerve Repair.** American Academy of Orthopaedic Surgeons at San Diego. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

October 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

October 1-5—**Second Annual Vascular Surgery Board Certification Review.** UCLA at Miramar Sheraton Hotel, Santa Monica. Monday-Friday.

October 6-13—**6th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott. Hawaii. One week.

October 9-14—**American Society of Plastic and Reconstructive Surgeons Inc., American Society of Maxillofacial Surgeons Inc. and Plastic Surgery Educational Foundation Meeting** at Las Vegas. Tuesday-Sunday. Contact: ASPRS-PSEF, Exec. Office, 233 N. Michigan Ave., Ste. 1900, Chicago 60601.

October 10-14—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. 34 hrs. $1,200.

October 11-13—**Controversies in Urology.** American Urological Association at San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, PO Box 25147, Houston, TX 77265. (713) 799-6070.

October 14-18—**Western Orthopedic Association Meeting** at San Diego. Sunday-Thursday. Contact: WOA, 1970 Broadway, Ste. 1235, Oakland 94612. (415) 893-1257.

October 14-18—**Preparing for Surgery: Medical Evaluation of the Preoperative Patient.** UCD at Doubletree Inn, Monterey. Sunday-Thursday.

October 17-21—**Advanced Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. $1,200.

October 21-26—**American College of Surgeons Meeting** at San Francisco. Sunday-Friday. Contact: ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 24—**Spinal Update 1984.** UCSF at Hyatt Regency Hotel, San Francisco. Wednesday. 18 hrs. $295. Contact: UCSF (415) 666-5731.

October 26-29—**Total Knee and Hip Arthroplasty "Hands On" Course.** Center for Health Education, Long Beach. Friday-Monday. 20 hrs. Contact: Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 27—**Lumbar Spine and Pelvis.** UCSD at Hotel del Coronado, Coronado. Saturday.

October 28-November 9—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 29-November 3—**Basic Microsurgery Training Workshop.** UCSD at Surgery Research Lab, University Hospital, San Diego. Monday-Friday. $1,200.

November 9-10—**American Academy of Facial Plastic & Reconstructive Surgery: Soft Tissue Workshops.** The San Francisco Head and Neck Surgery Foundation at Holiday Inn Union Square, San Francisco. Friday-Saturday. Contact: Cynthia Ashe, SFHNSF, 350 Parnassus Ave., Suite 502, San Francisco 94117. (415) 221-8487.

November 12-16—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday,

November 28-December 2—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday.

(Continued on Page 276)

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Other Programs: Christian Psychiatric Unit; 24 Hour Crisis Intervention Service; Psychiatric Emergency Team

For further information about Charter Baywood or admission procedures, contact:

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Leon Marder, M.D.
Hospital Administrator: Diana Goulet

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Beds: 86
Psychiatric Staff: 15
Programs: Adult and Adolescent Psychiatric; Adult Addictive Disease.

Other Programs: Women's Program; Eating Disorders; and Christian Psychiatric

For further information about Charter Grove or admission procedures, contact:

Medical Director: William Cohen, M.D.
Hospital Administrator: Jim Fridlington

Charter Oak Hospital

1161 East Covina Blvd.
Covina, California 91724
(213) 966-1632

Beds: 74
Psychiatric Staff: 14
Programs: Adult, Adolescent and Child Psychiatric; Adult Addictive Disease

Other Programs: Premenstrual Syndrome Clinic

For further information about Charter Oak or admission procedures, contact:

President of Medical Staff:
Adib Bitar, M.D.
Hospital Administrator: Jim Sholes

Charter Pacific Hospital

4025 West 226th St.
Torrance, California 90505
(213) 373-7733

Beds: 96
Psychiatric Staff: 36
Programs: Adolescent, Child and Young Adult Psychiatric; Adult and Adolescent Addictive Disease

Other Programs: Pediatric Neuro/developmental Diagnostic Unit; Charter Clinic, in Santa Ana, offers Neuropsychological child and adolescent services.

For further information about Charter Pacific or admission procedures, contact:

Director of Adolescent Unit:
Michael J. Levine,
Hospital Administrator: Jim Hackett

CHARTER MEDICAL CORPORATION

(Continued from Page 273)

OF INTEREST TO ALL PHYSICIANS

August 17-19—**Nutrition, Obesity, and Weight Control—White Water Raft Conference.** Mercy Medical Center, Redding at Klamath and Salmon Rivers. Friday-Sunday. 10 hrs. $295. Contact: Jerry Fikes, RN, Mercy Hospital, PO Box 6009, Redding 96099.

August 20-24—**CRYO '84: Course of Freezing of Animal Cells, Tissues and Organs.** UCD. Monday-Friday.

August 24-26—**Weekend Workshop on Stress for Physicians and Spouses.** CMA at El Encanto Hotel, Santa Barbara. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

September 1—**Medical Mycology.** UCSF. Saturday.

September 8-9—**Dermatopathology Board Review.** UCSF. Saturday-Sunday.

September 13-14—**Intensive Course in Adolescent Obesity.** UCSF. Thursday-Friday. $135.

September 17-19—**Relational Issues of Addiction: Violence, Sexuality and Intimacy.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, Conf. Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

September 17-21—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

September 19-21—**State of the Art in the Care of Geriatric Patients: Pre-Intra-Post-Operative Management.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $325. Contact: Robin B. Jackson, Office of Cont. Ed., PO Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

September 19-23—**Annual Scientific Program and Postgraduate Course of the Pacific Coast Fertility Society** at Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

September 20-23—**34th Annual Obesity and Associated Conditions Symposium.** American Society of Bariatric Physicians at MGM Grand Hotel, Reno. Thursday-Sunday. 17 hrs. Contact: Randall B. Lee, Exec. Dir., 4730 E. Caley Ave., Ste. 210, Englewood, CO 80111. (303) 779-4833.

September 21—**Dermatology and Dermatologic Office Procedure Workshop.** CME at Kona Kai Club, San Diego. Friday. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 23—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. $175. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 28-30—**Stress and Coping: A Weekend Workshop for Lesbian Physicians.** CMA at Stanford Sierra Lodge, South Lake Tahoe. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

September 29—**Food Allergy: Update 1984.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Geri Coldewey, LASACI, 1626 North Wilcox, #557, Hollywood 90028.

October 1—**Nutrition Symposium.** UCSF at Yosemite. Monday.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Tuesday.

October 8-19—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

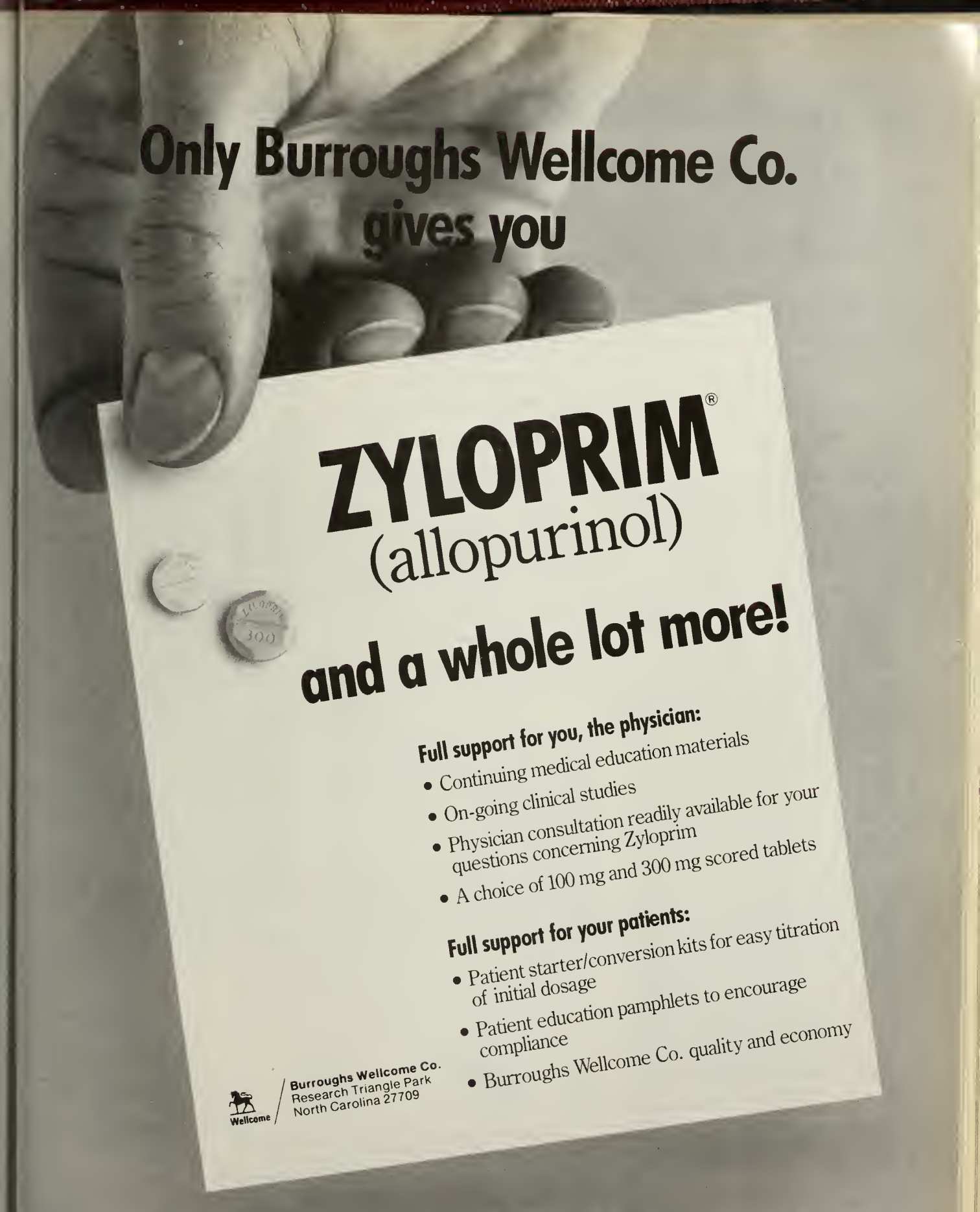
October 11-14—**A California Conference in Applied Clinical Geriatrics.** UCD at Napa Valley. Thursday-Sunday.

October 12-13—**Skin From A to Z.** UCSF. Friday-Saturday.

October 12-13—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $200.

October 12-14—**28th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Holiday Inn Golden Gateway, San Francisco. Friday-Sunday. 10 hrs. Contact: Joe Donovan, c/o

(Continued on Page 282)



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GENERAL INTERNIST, Board certified/eligible. Multi-specialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact A. J. Grose, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103

HEALTH OFFICER—Natrona County Board of Health invites applications for County Health Officer. Required MD, eligibility for licensure in Wyoming, MPH degree or five years experience as a paid physician in preventive medicine and environmental health. 70,000 population located in the heart of prime hunting and fishing. Salary $50,000 to $65,000 depending on qualifications and experience. Excellent fringe benefits. Send curriculum vitae by September 1, 1984, to Search Committee, Health Department, 1200 E. 3rd, Casper, WY 82601. EOE

WANTED FAMILY PRACTITIONER(S). Gateway to the Oregon Caves. 15,000 plus residents in lovely valley. Excellent referral system. 29 miles from hospitals. Enjoy the excitement of a rural family practice and time to spend outdoors. Board of Directors anxious to expand to meet community needs. Now available, one-half fully equipped modern clinic. Room for one or two physicians with excellent expansion potential. Expansion could be emergency type care or convalescent home. Call AC (503) 592-3916 or 592-2224 evenings or weekends.

THE OFFICE OF WORKERS' COMPENSATION PROGRAMS is seeking Board eligible/certified physicians to provide second opinion evaluations. Specialties include Orthopedics, ENT, Psychiatry, Cardiology, and Neurosurgery/Neurology. Locations include the San Francisco Bay Area, the Greater Los Angeles Area, San Diego, and Las Vegas. A contracted second opinion physician is precluded from also providing referee exams and is subject to fee schedule. Please send curriculum vitae to: Gerald T. Cullen, Contracting Officer, Office of Workers' Compensation Programs, US Dept. of Labor, 450 Golden Gate Ave., P.O. Box 36066, San Francisco, CA 94102.

BOARD CERTIFIED Oncologist, Cardiologist, Internist, Neurosurgeon, Otorhinolaryngologist for Southeastern Washington—Tri-Cities, 150,000 population. Outdoor activities abound. Group or solo opportunities. Contact Vesta Skiens, Kennewick General Hospital; (509) 586-6111 (309).

INTERNIST, CALIFORNIA, two American trained, Board certified General Internists seek the same for association in busy practice in Central San Joaquin Valley city of 50,000. No investment required. Subspecialist with interest in doing some general Internal Medicine desirable. Excellent recreational area with access to San Francisco, Yosemite and coast. Opportunity to establish a busy independent practice with no initial investment. Reply to: Box 6434, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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CIGNA Healthplans of California is offering a career opportunity to General and Family Practitioners with acute and preventive medicine orientation. Our HMO provides a personal patient population and a continuity of care as well as an excellent compensation package. Send curriculum vitae to:

Director Physician Recruitment

CIGNA Healthplans of California
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Glendale, CA 91203

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ALBUQUERQUE, NEW MEXICO: 2 positions opening for Emergency Room Physicians beginning August 1, 1984. Family Practice/Internal Medicine or Surgical Training acceptable if Board Certified or eligible. Rotate between suburban hospital and downtown Level II trauma center. 144 hours per month. Competitive salary plus benefits. Please call/write Jeff Sollins, MD, Medical Emergency Services, Presbyterian Hospital c/o ER, 1100 Central SE Albuquerque, NM 87102, (505) 841-1125 8-4 pm.

PHYSICIANS WANTED

FAMILY PRACTICE—NORTH IDAHO: ABFP or eligible to join low-key, but busy practice, excellent and beautiful family area. Lab, x-ray on premises, 24 hour ER coverage. Terms negotiable. Call (208) 773-1577 or respond with CV to 2209 Canyon Dr, Coeur d'Alene, ID 83814.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 234-4795, or send CV to EMP, P.C., PO Box 3398, Casper, WY 82602-3398.

SOUTH DAKOTA: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 234-4795, or send CV to EMP, P.C., PO Box 3398, Casper, WY 82602-3398.

OCCUPATIONAL MEDICINE PHYSICIAN: Santa Barbara County Health Care Services. Full-time position. Board certified/eligible Occupational Medicine. Clinical and Administrative responsibilities. Send CV to Gary Erbeck, MPH, Santa Barbara County Health Care Services, 315 Camino del Remedio, Santa Barbara, CA 93110.

RADIOLOGIST—Board eligible or certified, well versed in General Radiology, Realtime Ultrasound, Nuclear Medicine and CT. Excellent growth and future in active office and hospital practice—Contact (209) 222-3357. Temporary locum tenens considered.

POSITION AVAILABLE IN GENERAL INTERNAL MEDICINE. Community offers ideal family living in town of 12,000 people. Liberal fringe benefits—life insurance, health insurance, 30 days vacation plus 15 days sick leave each year. Complete malpractice insurance coverage provided. An unexcelled opportunity to engage in a challenging medical practice in a rural setting offering unlimited recreational opportunities—hunting, fishing, skiing, plus fresh clean air in abundance. Contact: P. J. Shannon, Chief, Personnel Service, VA Medical Center, Miles City, MT 59301. Telephone: (406) 232-3060, ext. 201. An Equal Opportunity Employer.

GENERAL SURGEON, SUN VALLEY, IDAHO. Energetic general surgeon to practice with multi-specialty group. Well equipped adjacent hospital. Quality of life high, income moderate. Curriculum vitae and references with first letter please. Dr Lynn T. Levy, PO Box 66, Sun Valley, ID 83353.

FAMILY PRACTITIONER, BC/BE for challenging work with Community Clinic. 3 days per week plus call, OB included. Benefits. Send CV to Betty Arterberry, Personnel Officer, Sonoma County Indian Health Project, Inc., 2240 Professional Drive, Santa Rosa, CA 95401.

OBSTETRICIAN GYNECOLOGIST—Board certified or eligible—to join multispecialty group. Hospital facilities adjacent. Gateway to San Juan Islands. Excellent recreational opportunities. Send CV to: Dr Harold Clure, Family and Internal Medicine Associates, 24th & M Avenue, Anacortes, WA 98221, or call (206) 293-3101.

(Continued on Page 280)

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(Continued from Page 278)

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Director of Physician Services
CHEC Medical Centers, Inc.
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PARTNER NEEDED for San Francisco area practice—New, primary care clinic fifteen miles south of San Francisco seeks BE/BC FP, IM or EM physician. No buy-in, guaranteed compensation plus incentives, regular hours. Malpractice, health insurance, plus other fringes. Ideal for MD who wants private practice with strong management and financial support. Send CV to Michael Goluska, MD, Serramonte Medical Bldg., Suite 201, 1500 Southgate Blvd., Daly City, CA 94015.

SANTA BARBARA: need qualified primary care physicians for urgent care centers. Excellent referral base and community support. No nights, share weekends, evenings, holidays. Attractive seaside resort. Great restaurants, schools, water sports, UC campus. Competitive salary, fringes, stock option. Contact Rebecca Horton, The MedCenter, 2954 State, Santa Barbara, CA 93105, (805) 682-7411.

WANTED: Family practitioners who are Board certified or Board eligible and/or have at least two years of related clinical experience. Will provide ambulatory services in a primary care program consisting of a central primary care center and six satellite clinics. The clinical facilities include laboratory, x-ray and pharmacy support services to allow for a comprehensive range of diagnostic and treatment capabilities. Responsibilities will include the clinical supervision of family nurse practitioners, sharing of on-call assignments, in addition to providing ambulatory medical care to a general population. The salary and fringe benefits are competitive. This program is under the direction of the Sacramento County Health Department. For further information, contact Dr. Peter Kho, Medical Director, Clinic Services Branch, Sacramento County Health Department, 3701 Branch Center Road, Sacramento, CA 95827, or call (916) 732-3687.

GENERAL PRACTITIONERS—Specialists—Full-time positions or Locum Tenens. If you're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

JOIN A FAMILY PRACTICE IN BEAUTIFUL CENTRAL CALIFORNIA—Central California Faculty Medical Group seeks Board Certified Family Physicians for a new Private Family Practice (OB and Inpatient). Rapidly growing metropolitan area, Sierra mountain recreation, attractive remuneration, and opportunity to participate in teaching programs. Send CV to H. John Blossom, MD, Central California Faculty Medical Group, 1921 N. Gateway Blvd., Fresno, CA 93727.

SEATTLE—Family Physician needed to join other Family Physicians in multispecialty group. Dynamic outpatient clinic with multiple support services. Reasonable night call and some inpatient opportunities. Excellent benefits and competitive salary. Contact Ramon Sanchez, MD or Case Kolff, MD; (206) 762-3730.

STAFF PSYCHIATRIST—Spokane Community Mental Health Center seeks board-eligible staff psychiatrist to join five full-time psychiatrists and large multidisciplinary staff. Varied duties include consultation, staff supervision, and direct service, primarily with chronically mentally ill. Programs for this population include Fountain-House-type club, medication clinics, and intensive short-term day programs. Spokane, in beautiful NW setting, population 348,000, is a low-cost-of-living area and superb place to raise family. Salary $59,000, plus excellent benefits. Inquire: Executive Director Mary Higgins or Dr. Tad Patterson, Spokane CMHC, S. 107 Division, Spokane, WA 99202, or call collect, (509) 838-4651. EOE.

UROLOGIST, ORTHOPAEDIC SURGEON, OBSTETRICIAN/GYNECOLOGIST AND NEUROLOGIST to join progressive multi-specialty clinic in sunny southeastern New Mexico. Modern facility, family oriented community of 40,000, service area 125,000. Good salary plus incentive bonus paid on production. Many excellent benefits including insurance, paid vacations and continuing education, stock option offered. Immediate openings, call (505) 392-5571, or send CV to Melba Greer, Recruiting Director, Norte Vista Medical Center, Ltd., 2410 North Fowler, Hobbs, NM 88240.

ALASKA—Opportunities for board certified or eligible Family Practitioner, Pediatrician, and Orthopedic Surgeon in multi-specialty 20-physician group in Fairbanks. An opportunity to practice quality medicine in a unique setting in the heart of Alaska's interior with outstanding outdoor recreational opportunities. Fairbanks is a community of 30,000 with a trading population of 65,000. Clinic located two miles from modern 183-bed community hospital and four miles from the cultural center, University of Alaska campus. Excellent compensation and benefit package. No immediate investment. Excellent growth potential for energetic individual. First year salary guarantee with incentive. Send curriculum vitae to Ron Davis, Manager, Tanana Valley Clinic, 1001 Noble Street, Fairbanks, AL 99701.

CALIFORNIA, SAN JOSE: Established group has full and part-time positions available for physicians with experience in Emergency Medicine and Family Practice to staff Acute Care Clinic at teaching hospital and a new low-volume Emergency Department. Minimum Guarantee plus Fee-for-Service. Contact James B. Lane, MD, 1625 The Alameda, #201, San Jose, CA 95126; Phone: (408) 293-8881.

UNIQUE OPPORTUNITY in prime recreational area in Southern Utah surrounded by National Parks, small college town with easy access to Salt Lake City or Las Vegas. Hospital-based physician group seeking BOARD-certified/eligible internist with interest in cardiology and/or critical care medicine, general surgeon and OB/GYN. Excellent opportunity for aggressive, independently-minded physician(s) to fill a need for specialty care. Initial financial support available. Direct inquiries to: Marcus Kuypers, MD, Valley View Medical Center, 595 South 75 East, Cedar City, UT 84720, (801) 586-6587.

CALIFORNIA—Growing family practice group needs Board Certified FP with OB skills in Mountainous Resort Area—Send inquiries to Randall Meredith, MD, P.O. Box 1880, Weaverville, CA 96093.

WANTED INFECTIOUS DISEASE SPECIALIST BE/BC to join two in challenging practice limited to Infectious Disease. San Francisco Bay Area. Salary with incentive leading to partnership. Send CV to IDMG, 2425 Larkin, Suite 2, San Francisco, CA 94109.

WANTED: University trained general surgeon to join three other general surgeons in 14-physician clinic. Location: southern Idaho. Surrounding area abounds in recreational opportunities. Applicant must have excellent qualifications. Send résumé to Box 1233, Twin Falls, ID 83301.

TWO BOARD CERTIFIED INTERNISTS looking for a third trained Board Certified/Board Eligible Internist for busy practice in Central San Joaquin Valley. Please reply to Box 6438, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

CALIFORNIA, SAN JOSE: Position available for Board Prepared/Board Certified Emergency Physician with established group in the San Francisco Bay Area in a high volume university-affiliated teaching hospital and a large community hospital with recently established Trauma Service. Fee-for-Service compensation/minimum guarantee. Contact James B. Lane, MD, 1625 The Alameda, #201, San Jose, CA 95126. Phone: (408) 293-8881.

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NEPHROLOGIST WANTED to cover Renal Practice and Dialysis Unit in Vallejo, CA. For vacation August 13-29. Salary plus housing may be available. Contact: Peter Philbin, MD; (707) 554-1170 days.

RADIOLOGIST: Board certified to cover office/hospital vacation or leave time. CT/US plus 12 years experience. New to Los Angeles but will travel; (818) 907-0136.

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... offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

DIAGNOSTIC RADIOLOGIST desires situation in small hospital (25-50 beds) CT and Ultrasound (real time). Willing to do some locums. Licensed in California, Oregon and Washington. Please reply Box 6436, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

ORTHOPAEDIC PRACTICE, ORANGE COUNTY, CALIFORNIA, adjacent to major hospital, five additional hospitals in 5-mile radius, will aid in transition. Box 4191, Irvine, CA 92714.

ALLERGY, SAN FRANCISCO BAY area. Seller plans to retire at end of 1984. 85% of practice concerns environmentally induced illnesses, 15% Forensic Medicine. Buyer must be Board certified in Allergy and Immunology or Toxicology and have extensive post graduate training and experience in clinical ecology. Strong research and academic background essential. Income has averaged 450-K over the past 5 years. Easy terms. For further information please write Box 6437, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

MONTANA—Progressive 30-physician multispecialty group has outstanding practice opportunities for the following specialties: Allergy, Endocrinology, Infectious Disease, Gastroenterology, Otolaryngology, Psychiatry and Orthopaedic Surgery. For further information, contact Wyman Taylor, Administrator, Great Falls Clinic, PO Box 5012, Great Falls, MT 59405 or (406) 454-2171.

Practice Opportunities in San Francisco Bay Area

For qualified primary care physicians. Full or regular part time positions available. Fee for service, with minimum hourly guarantee. Physicians must be able to provide complete family health care. Board certification preferred. For more information, contact:

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MedWest
33 Quail Court, Suite 200
Walnut Creek, CA 94596
(415) 947-1181

FAMILY PRACTICE OPPORTUNITY in beautiful rural community in Sierra foothills. Close to large metropolitan areas and mountains. Excellent recreational opportunities. Close proximity to hospital. Good call coverage. Send inquiries to Box 6439, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

SOUTHERN CALIFORNIA FAMILY MEDICAL PRACTICE FOR SALE. Idyllic location near ocean in beautiful Santa Barbara. Gross $150,000. Physician owner must leave country for family reasons. Call (805) 967-9668 or (805) 965-4531.

LONG ESTABLISHED DERMATOLOGY PRACTICE in new complex adjacent to hospitals in Northern California coastal city of Eureka. Opportunity exists, upon approval of partners, to join partnership operating complex providing tax and rental advantages. Area offers "no stress" environment close to hunting, fishing and ocean beaches. Contact Joan Evans, Bus. Mgr.; (707) 443-2268 or (707) 442-1388.

CALIFORNIA AND WESTERN STATES. HIGH INCOME practices for sale: Ophthalmology, Orthopedics, Radiology, OB/GYN, Psychiatry, Internal, Family, Pediatric, others. Mary Bradshaw, Professional Practice Opportunities, 21 Altamount Drive, Orinda, CA 94563; (415) 376-0762. Sales, Appraisals, Consulting, Placement, Résumé preparation service.

MEDICAL OFFICE SPACE available for lease 1,075 sq ft in Berkeley near Alta Bates Please call The Berkeley Central Medical Building at (415)848-5137.

OFFICE SPACE—Available in well established,diversified medical-dental-pharmacy building. Good San Francisco Bay Area location in Pleasant Hill. Easy access to freeway Ownership an option. For more information call (415)689-4404 or (415)676-8485.

SILICON VALLEY—Space available in multi-disciplinary,well-run,computerized office near hospital High income,high growth region. Rent on percentage basis possible Kenneth Peters, MD, 515 South Dr., Suite 15, Mountain View,CA 94040;(415)961-9430.

MISSION VIEJO,CALIFORNIA: Time share medical office suite available 3 half-days per week Respond to Box 6428,Western Journal of Medicine,44 Gough St., San Francisco,CA 94103.

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PART-TIME MEDICAL CONSULTANT: CONTRACTS

Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 100 Van Ness Avenue, San Francisco, CA. No patient contact. Administrative and Congressional decisions will affect the number of physicians and specialties needed. Applicants must: (1) have a valid license to practice medicine in the USA, (2) have recent or current clinical experience; and (3) be available at some time between 7:00 A.M. and 5:30 P.M., Monday through Friday for case review. Generally, contractors must perform reviews for at least eight and not more than twenty hours per week, although exceptions may occur in shortage areas. Subject to change, the following specialties are most apt to be needed: Psychiatry, Cardiology, Orthopedics, Pulmonary Medicine with expertise in pulmonary function testing.

Please submit a current and complete curriculum vitae (CV) including the following information which will be used for ranking and selection:

1. *Medical Training*

   Identify specialty, training facility, dates, and number of years in specialty. Please indicate if you are Board eligible or certified and in what specialty.

2. *Medical Experience (Current and Past)*

   A. Clinical Practice

      Identify dates, location and nature of clinical practice and experience and whether full-time or part-time.

   B. Other Experience

      Identify other professional activities and experience such as teaching, publications, involvement with committees and professional organizations, etc.

3. *Disability Claims Experience,* reviewing evidence of record in order to evaluate claims for benefits:

   A. Type of claims
   B. Agency
   C. From_____ To _____
   D. Approximate number of claims reviewed.

4. *Availability*

   Approximate hours and days available for case review:

   M_____ Tu_____ W_____ Th_____ F_____

   When addressing availability; please indicate the maximum in terms of BOTH days and hours that you would be available if requested by the SSA.

In addition to physicians for medical review, a chief medical consultant (Regional Medical Advisor) contractor is needed. This consultative and advisory contract includes training of medical consultant contractors in accordance with Government provided procedures and content areas, providing medical advice to program staff, and consulting on SSA policy relative to medical review of disability cases, and providing information to State Agencies, etc. To qualify for this contract, offerers must meet the criteria for the part-time medical consultant position; additionally, past experience in a similar responsible position is required which should include training of physicians and evaluating medical or disability claims. Applicants must submit a CV as defined above. Additional weight will be given to: administrative experience, leadership and management experience, and experience relative to review processes such as the type contemplated in this announcement. Applicants for this position should be available approximately 20 hours per week.

Selection for all contracts will be based on information included in the CV. Preference will be given to individuals in current clinical practice whose training, background, experience and availability best suit the needs of the disability program. As flexibility in work hours is necessary, those physicians applying who live outside the commute area must provide positive evidence that the estimated hours and days cited for availability can actually be fulfilled in the San Francisco Regional Office.

Please indicate on your CV if you are applying for the medical review or chief medical consultant position. Please provide every item of information, in addition to your name, current address and phone number, NOT LATER THAN 8/20/84 to:

Contracting Officer
Department of Health and Human Services
Division of Administrative Services
Regional Acquisition Management Branch
50 United Nations Plaza, Room 403
San Francisco, California 94102

For questions concerning the contracts, call (415) 556-3050. Inquiries about the nature of the work, call (415) 556-2756.

We encourage applications from women and minorities, and would appreciate it if readers of this notice would bring it to the attention of others who may be qualified.

(Continued from Page 276)

WOMA, 433 Palmer Ave., Aptos 95001. (408) 688-0667.

October 15-18—**9th Annual Family Practice Update.** LLU. Monday-Thursday.

October 16-18—**Primary Medical Care of Selected Infectious Diseases.** Health Science Seminars of UCSF at Sheraton Hotel, Poipu Beach, Kauai, HI. Tuesday-Thursday. $225. Contact: Cynthia Vaughan, Program Coordinator, PO Box 22023, San Francisco 94122. (415) 861-2713.

October 17—**Second Annual Alcohol & Drug Dependencies Symposium.** Kaiser Permanente Southern California at The Pasadena Hilton, Pasadena. Wednesday. $90. Contact: Judy Harrison—Dept. of Clinical Services, Kaiser-Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 18-21—**Clinical Biofeedback Certificate Program.** UCLA. Thursday-Sunday.

October 19-21—**Medical Mycology.** UCSF. Friday-Saturday.

October 22-25—**Primary Care Update: 69th Scientific Assembly of Interstate Postgraduate Medical Association** at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: H. B. Maroney, (608) 257-6781.

October 25-27—**Postgraduate Institute.** CMA at Monterey Sheraton, Monterey. Thursday-Saturday. $150—Non-member, $100—Member. Contact: Janice Rigney (415) 863-5522 Ext. 416.

October 26-28—**Weekend Workshop on Stress for Physicians and Spouses.** CMA at Holiday Inn, Napa. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

October 29-November 1—**Interstate Postgraduate Medical Association Meeting** at Las Vegas. Monday-Thursday. Contact: H. B. Maroney, Exec. Dir., PO Box 1109, Madison, WI 53701. (608) 257-6781.

November 9—**New Concepts in Medicine—20th Annual Staff Seminar.** California Hospital Medical Center, Los Angeles. Friday. (213) 748-2411.

(Continued on Page 284)

RU-TUSS® II
sustained release capsules

Before prescribing, see complete prescribing information. The following is a brief summary.
DESCRIPTION: Each sustained release capsule contains 12 mg of chlorpheniramine maleate, USP and 75 mg of phenylpropanolamine hydrochloride, USP in a base to provide prolonged activity.
INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis and vasomotor rhinitis, including nasal obstruction (congestion).
CONTRAINDICATIONS: Hypersensitivity to any of the components, concurrent MAO inhibitor therapy, severe hypertension, bronchial asthma, coronary artery disease, stenosing peptic ulcer, pyloroduodenal or bladder neck obstruction. Do not use in children under 12 years.
Do not use this drug in patients with narrow-angle glaucoma, obstructive or paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Do not use in nursing mothers.
Use in treating lower respiratory tract symptoms, including asthma, is contraindicated.
WARNINGS: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients. Patients should also be warned about the possible additive effects of alcohol and other CNS depressants.
Usage in pregnancy: Safe use in pregnancy has not been established. Use only when the potential benefits have been weighed against the possible hazards to the mother and child. Note that an inhibitory effect on lactation may occur.
PRECAUTIONS: Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, hypertension, hiatal hernia with reflux esophagitis, intestinal atony of the elderly or debilitated intestinal obstruction, myasthenia gravis, renal impairment, and ulcerative colitis (severe).
Drug Interactions: MAO inhibitors, alcohol or CNS depressants, especially anesthetics, barbiturates, and narcotics.
ADVERSE REACTIONS: Prolongs the response to nervous stimulation, potentiates the response to norepinephrine, and inhibits the response to tyramine.
Slight to moderate drowsiness occurs relatively infrequently with chlorpheniramine maleate. Other possible side effects common in antihistamines in general include perspiration, chills, dryness of mouth, nose and throat.
Cardiovascular System: Hypotension, hypertension, headache, palpitations, tachycardia, extrasystoles.
Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis, leukopenia.
Nervous System: Sedation, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesias, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis hysteria, neuritis, convulsions.
Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.
Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.
Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.
DOSAGE AND ADMINISTRATION: Dosage should be individualized according to the needs and response of the patient. Adults: one capsule every 8 to 12 hours not to exceed 3 capsules daily. Not for use in children under 12 years of age.
OVERDOSAGE: Treatment of the signs and symptoms of overdosage is symptomatic and supportive. In the event of overdosage, emergency treatment should be started immediately.
Treatment: The patient should be induced to vomit, even if emesis has occured spontaneously. Vomiting by the administration of ipecac syrup is a preferred method. However, vomiting should not be induced in patients with impaired consciousness. Stimulants (analeptic agents) should not be used. Vasopressors may be used to treat hypotension. Short-acting barbiturates, diazepam or paraldehyde may be administered to control seizures. Hyperpyrexia, especially in children, may require treatment with tepid water sponge baths or a hypothermic blanket. Apnea is treated with ventilatory support.
HOW SUPPLIED: Green and clear capsules with green and white beads. Bottles of 100 tablets. NDC 0524-0031-01
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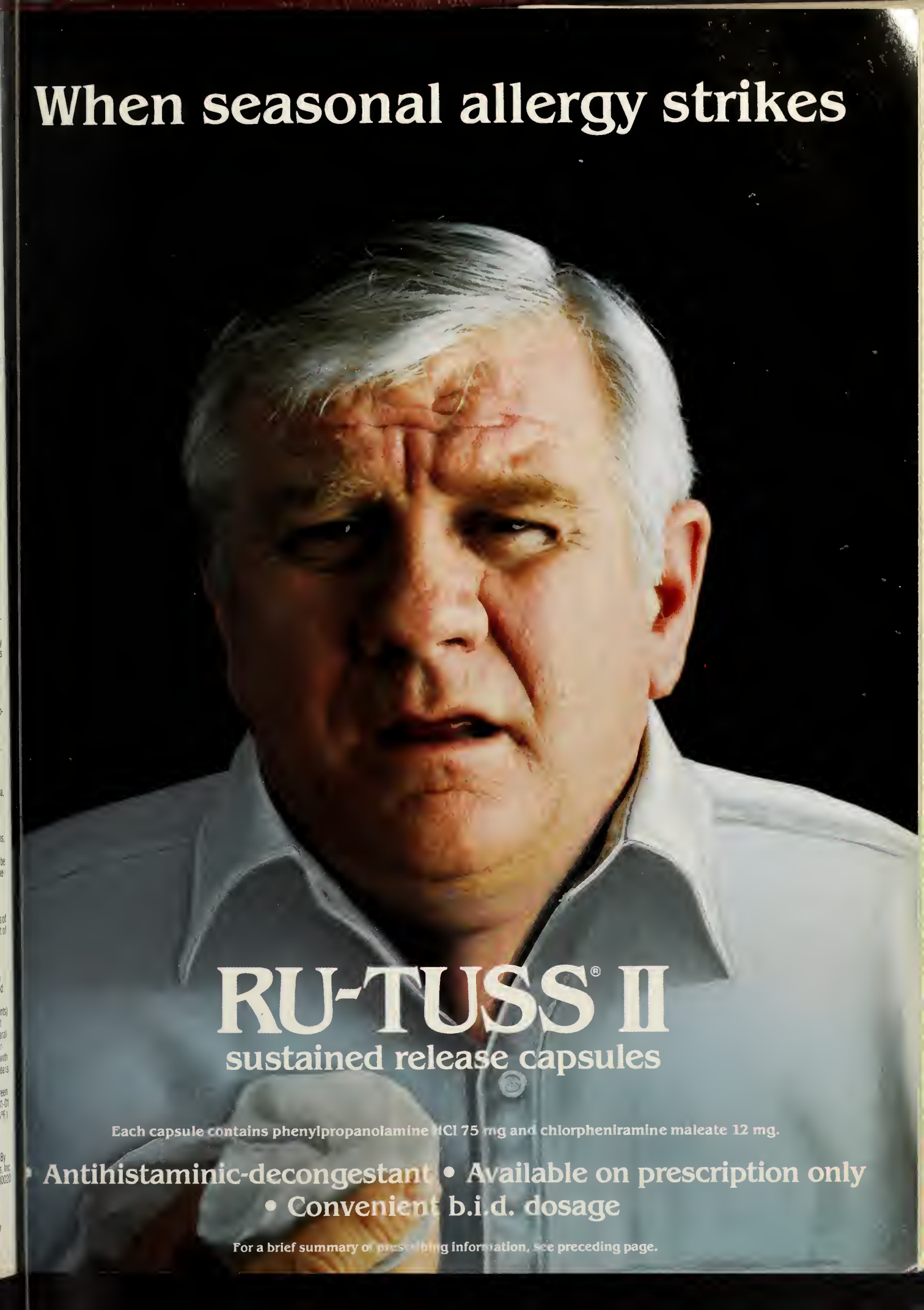

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For a brief summary of prescribing information, see preceding page.

(Continued from Page 282)

November 9-11—**Hawaii Medical Association Annual Meeting** at Kauai Surf Hotel, Kauai. Friday-Sunday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu, HI 96814. (808) 536-7702.

November 18—**16th Annual Symposium: "The Newest Concepts in Clinical Practice."** Granada Hills Community Hospital & UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Carol Smith, Granada Hills. (818) 360-1021.

November 30-December 2—**Weekend Workshops on Stress for Physicians and Spouses.** CMA at La Playa Hotel, Carmel. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

IDAHO

August 15-21—**Updates in Pediatrics: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 18-19—**Trauma Update—84.** North Shore Convention Center, Lake Coeur d'Alene. Contact: Linda Ady, Conf. Coordinator, Idaho EMS System, 450 W. State St., Boise 83720. (208) 334-4245.

September 9-14—**Up-to-Date Cardiac Therapy: An EPIC Medical Expedition.** Rafting on the Middle Fork of the Salmon River. Sunday-Friday. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 18-24—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** Fishing and Chukar hunting adventure on the Main Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

September 21-22—**American College of Physicians—Regional Meeting.** Heritage Inn, Great Falls. Friday-Saturday. Contact: Warren D. Bowman, Jr, MD, Billings Clinic, Box 2555, Billings 59103.

October 4-6—**Montana Medical Association Annual Meeting.** Sheraton, Billings. Thursday-Saturday. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000.

NEW MEXICO

The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category I under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (500) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 26-31—**Abandonment.** Abiquiu. Sunday-Thursday. Ghost Ranch. 36 hrs. NM Cat. IV. Contact: Chicago Society of Jungian Analysts, Inter-Regional Society of Jungian Analysts, 1520 Cerro Gordo Rd., Santa Fe 87501. (505) 982-5693.

September 13-15—**Concepts and Controversies in Perinatal Care.** Albuquerque. Thursday-Sat-

(Continued on Page 286)

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 7—Edited by W. Maxwell Cowan, Salk Institute for Biological Studies. Annual Reviews Inc, 4139 El Camino Way, Palo Alto, CA 94305, 1984. 478 pages, $27.00.

THE ART OF CORRECTIVE MAKEUP—How to Camouflage Unattractive Scars and Blemishes—Linda Seidel and Irene Copeland. Doubleday & Company, Inc, 245 Park Ave, New York, NY 10167, 1984. 177 pages, $15.95.

BODY CT—A HANDBOOK—Adrian K. Dixon, MA, MRCP, FRCR, Lecturer in Radiology, University of Cambridge, and Honorary Consultant, Addenbrooke's Hospital, Cambridge, England. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1983. 163 pages, $24.00 (paperback).

CHEMOTHERAPY OF GYNECOLOGIC CANCER—Editor: Gunter Deppe, Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit. Alan R. Liss, Inc, 150 Fifth Ave, New York, NY 10011, 1984. 389 pages, $58.00.

THE CLINICAL NEUROSCIENCES—Volumes 1 & 2—NEUROLOGY/NEUROSURGERY—Editor: Roger N. Rosenberg, MD, Professor of Neurology and Physiology and Chairman, Dept of Neurology, University of Texas Health Science Center at Dallas, Southwestern Medical School, and Chief, Neurological Services, Parkland Hospital and Children's Medical Center, Dallas; Associate Editor: Robert G. Grossman, MD, Professor and Chairman, Dept of Neurosurgery, Baylor College of Medicine, and Chief, Neurosurgical Service, The Methodist Hospital, Houston; with 27 contributors. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 1,497 pages. $525.00 for 5 volumes.

THE CLINICAL NEUROSCIENCES—Volume 3—NEUROPATHOLOGY—Editor: Roger N. Rosenberg, MD, Professor of Neurology and Physiology, Chairman, Dept of Neurology, University of Texas Health Science Center at Dallas, Southwest Medical School, Chief, Neurological Services, Parkland Hospital and Children's Medical Center, Dallas; Associate Editor: Sydney S. Schochet, Jr, MD, Professor of Pathology (Neuropathology), Dept of Pathology, West Virginia University Medical Center, Morgantown; with 15 contributors. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 561 pages. $525.00 for 5 volumes.

THE CLINICAL NEUROSCIENCES—Volume 5—NEUROBIOLOGY—Editor: Roger N. Rosenberg, MD, Professor of Neurology and Physiology and Chairman, Dept of Neurology, University of Texas Health Science Center at Dallas, Southwestern Medical School, and Chief, Neurological Services, Parkland Hospital and Children's Medical Center, Dallas; Associate Editor: William D. Willis, Jr, MD, PhD, Professor, Departments of Anatomy and Physiology & Biophysics, and Director, Marine Biomedical Institute, University of Texas Medical Branch at Galveston; with 28 contributors. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 626 pages. $525.00 for 5 volumes.

COELIAC DISEASE—W. T. Cooke, MD, FRCP, Honorary Consultant Physician and Gastroenterologist, The General Hospital, Birmingham, and G. K. T. Holmes, MD, MRCP, Consultant Physician and Gastroenterologist, Derbyshire Royal Infirmary, Derby, and Clinical Teacher in the University of Nottingham, England. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036. 276 pages, $55.00.

COMPLICATIONS OF TOTAL HIP REPLACEMENT—Edited by R. S. M. Ling, MA, BM(Oxon), FRCS, Consultant Orthopaedic Surgeon, Princess Elizabeth Orthopaedic Hospital, Exeter, UK. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 288 pages, $45.00.

COMPUTED TOMOGRAPHY OF THE KIDNEYS AND ADRENALS—Volume 3 in CONTEMPORARY ISSUES IN COMPUTED TOMOGRAPHY—Edited by Stanley S. Siegelman, MD, Professor of Radiology, Olga M. B. Gatewood, MD, Associate Professor of Radiology, and Stanford M. Goldman, MD, Associate Professor of Radiology, The Johns Hopkins University School of Medicine, Baltimore. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 281 pages, $39.50.

CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Eighth Edition—Edited by C. Henry Kempe, MD, Professor of Pediatrics and Microbiology; Henry K. Silver, MD, Professor of Pediatrics, and Donough O'Brien, MD, FRCP, Professor of Pediatrics, University of Colorado School of Medicine, Denver, and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 1,164 pages, $27.00.

GUIDE TO INTERPRETING 12-LEAD ECGs—J. Marcus Wharton, MD, Clinical Instructor in Medicine, University of California, San Francisco, and Chief Medical Resident, San Francisco General Hospital Medical Center; and Nora Goldschlager, MD, Clinical Professor of Medicine, University of California, San Francisco, and Director, Coronary Care Unit and Electrocardiographic Laboratory, San Francisco General Hospital Medical Center. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1984. 235 pages, $19.95, plus $1.50 handling (softbound).

IMMUNOLOGY OF PARASITIC INFECTIONS—Second Edition—Edited by Sydney Cohen, CBE, MD, PhD, PRCPath, FRS, Head, Dept of Chemical Pathology, Guy's Hospital Medical School, London, and Kenneth S. Warren, MD, DTM&H, Professor of Medicine, New York University School of Medicine, Adjunct Professor, Rockefeller University, and Director for Health Services, The Rockefeller Foundation, New York. Blackwell Scientific Publications, 1982. USA Distributor: Blackwell Mosby Book Distributors, 11830 Westline Industrial Drive, St Louis, MO 63141. 848 pages, $96.00.

THE MEDICAL INDUSTRIAL COMPLEX—Stanley Wohl, MD, Staff Member of Stanford University Medical Center, Stanford, California, and President, InfoMed Systems, Inc., San Francisco. Harmony Books, One Park Avenue, New York, NY 10016, 1984. 214 pages, $14.95.

MORAL DILEMMAS IN MEDICINE—A COURSEBOOK IN ETHICS FOR DOCTORS AND NURSES—Alastair V. Campbell, MA, BD, ThD, Senior Lecturer in Christian Ethics, University of Edinburgh. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 174 pages, $9.75.

THE PARENTS' EMERGENCY GUIDE: An Action Handbook for Childhood Illness and Accidents—The Diagram Group. Facts on File Publications, 460 Park Avenue South, New York, NY 10016, 1984. 127 pages, $6.95 (paperback).

PATHOLOGY OF THE EXTREMELY AGED—Volume 1: CENTENARIANS—Tokyo Metropolitan Institute of Gerontology—Editor: Yasukazu Tanaka, MD. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Court, St Louis, MO 63043, 1984. 97 pages, $22.50 (softbound).

THE PERIPATETIC DIABETIC—June Biermann and Barbara Toohey. Jeremy P. Tarcher, Inc, 9110 Sunset Blvd, Los Angeles, CA 90059, 1984. 252 pages, $14.95 (cloth); $7.95 (paper).

PRACTICAL DIAGNOSIS OF SOFT TISSUE TUMORS—Virginia A LIVolsi, MD, Professor of Pathology and Director of Surgical Pathology, University of Pennsylvania School of Medicine, Philadelphia; Maria J. Merino, MD, Director of Gynecologic Pathology and Assistant Professor of Pathology, Yale University School of Medicine, New Haven, Connecticut; and Michael L. Saruk, MD, Formerly Assistant Professor of Dermatology and Pathology, University of Pittsburgh School of Medicine. Medical Economics Books, 680 Kinderkamack Rd., Oradell, NJ 07649, 1984. 242 pages, $29.95.

PRIMARY AND SECONDARY IMMUNODEFICIENCY DISORDERS—Edited by Ranjit Kumar Chandra, MD, FRCP(C), Professor of Pediatric Research, Memorial University of Newfoundland; Director of Immunology Laboratory, Janeway Child Health Centre, St John's, Newfoundland; and Visiting Professor of Nutritional Immunology, Massachusetts Institute of Technology, Cambridge. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1983. 299 pages, $55.00.

RADIOLOGY IN EMERGENCY MEDICINE—Volume 3 in CLINICS IN EMERGENCY MEDICINE—Edited by Murray K. Dalinka, MD, Professor of Radiology, University of Pennsylvania Medical School, Philadelphia, and Jeremy J. Kaye, MD, Professor of Radiology, Associate Professor of Orthopedics and Rehabilitation and Director of Division of Diagnostic Radiology, Vanderbilt University Medical Center, Nashville, Tennessee. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 355 pages, $39.00.

RADIOGRAPHY OF THE HEAD—Pamela M. Kimber, FCR, SRR, Superintendent Radiographer, Wessex Neurological Centre, Southampton General Hospital, England. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1983. 197 pages, $26.50 (paperback)

REVIEW OF MEDICAL MICROBIOLOGY—Ernest Jawetz, MD, PhD, Professor of Microbiology and Medicine, Lecturer in Pediatrics, University of California School of Medicine, San Francisco; Joseph L. Melnick, PhD, Distinguished Service Professor of Virology and Epidemiology, Baylor College of Medicine, Houston, and Edward A. Adelberg, PhD, Professor of Human Genetics, Yale University School of Medicine, New Haven. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 557 pages, price not given (paperback).

RICHARD LOWER'S VINDICATIO**—A DEFENCE OF THE EXPERIMENTAL METHOD**—A facsimile edition introduced and edited by Kenneth Dewhurst, MD, FRHistS. Sandford Publications, Manor House, Sandford-on-Thames, Oxford OX4 4YN, Great Britain, 1983. 314 pages, price: 12 English Pounds, limited to 250 numbered and signed copies.

TESTIFYING IN COURT—A Guide for Physicians—Second Edition—Jack E. Horsley, JD; with John Carlova. Medical Economics Books, Oradell, NJ 07649, 1983. 142 pages, $22.95, plus $1.50 handling charge, available from Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205.

(Continued from Page 284)

urday. AMFAC Hotel. 13 hrs. NM and AMA Cat. I. Contact: Office of CME, UNM School of Medicine, Albuquerque 87131. (505) 277-3942.

October 4-6—**The 12 Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Savage Auditorium, Presbyterian Professional Building. 23 hrs. AMA and NM Cat. I. Contact: The New Mexico Heart Institute, 201 Cedar SE, #604, Albuquerque 87106. (505) 242-2796.

October 26—**Practice Marketing Techniques.** Albuquerque. Friday. Savage Auditorium, Presbyterian Professional Building. Credit hours pending. Contact: NM Society of Internal Medicine, 303 San Mateo NE, Ste. 204, Albuquerque 87108. (505) 266-7868.

October 27—**Computers in Medical Practice.** Albuquerque. Saturday. Savage Auditorium, Presbyterian Professional Building. Credit hours pending. Contact: NM Society of Internal Medicine, 303 San Mateo NE, Ste. 204, Albuquerque 87108. (505) 266-7868.

November 2—**Los Alamos Cancer Center Annual Program.** Los Alamos. Friday. Credit hours pending. Contact: Los Alamos Cancer Center, Los Alamos 87544. (505) 662-9620.

November 9-10—**New Mexico Medical Society Interim Meeting—Sports Medicine.** Clovis. Friday-Saturday. 6 hrs. AMA Cat. I, NM Cat. IV. Contact: NMMS, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 14-15—**ABCs of Chronic Pulmonary Disease in Children and Young Adults.** Albuquerque. Wednesday-Thursday. Savage Auditorium, Presbyterian Professional Building. 14 hrs. NM Cat. I. Contact: Roy Goddard, MD, Winrock Medical Center, Albuquerque 87110. (505) 883-8246.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. NM and AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

(Continued on Page 288)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 286)

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * *

EMERGENCY MEDICINE

November 15-16—**Symposium on Critical Care**

Medicine. Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

September 7-8—**The Ashland Conference: Immunology and Allergy in Primary Care.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

November 30-December 1—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 AM. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

September 7—**Infectious Disease Update** (Sponsor: University of Utah). Friday. Skaggs Hall, U of U, Salt Lake City. No fee. 6 hrs. Contact: Rosalie Lammle, (801) 581-8664.

November 30—**Sleep Disorders: A Clinical Approach** (Sponsor: University of Utah/Pulmonary Division, LDS Hospital). Friday. Marriott Hotel, Salt Lake City. Credit and fee to be announced. Contact: DuWayne Schmidt, MD, (801) 321-1100.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 17-23—(OREGON) **Psychiatry for Primary Physicians.** Friday-Thursday. Sunriver Resort, Sunriver. Contact: U/W.

August 29-September 4—(ALBERTA) **Scientific Aspects of the Art of Dance.** Banff Centre, Banff, Alberta. Contact: U/W.

(Continued on Page 292)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

In clinical anxiety,

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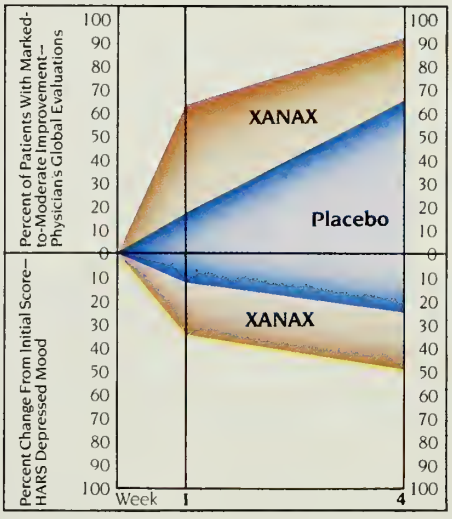
Kalamazoo, Michigan 49001 USA

depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

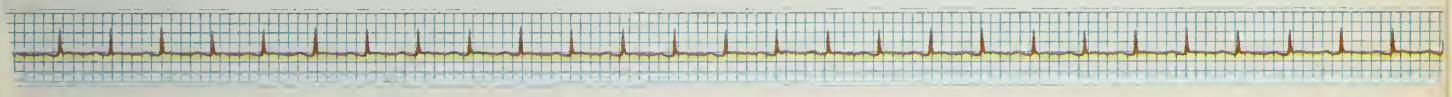
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).


Percent of Patients With Marked-to-Moderate Improvement–Physician's Global Evaluations
Percent Change From Initial Score–HARS Depressed Mood
XANAX
Placebo
XANAX
Week 1
4
100 90 80 70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80 90 100

A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy



- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file. The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets

alprazolam IV

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests.* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility.* No carcinogenic potential or impairment of fertility in rats. *Pregnancy.* See Warnings. *Nonteratogenic Effects.* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery.* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence. Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class.* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

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Kalamazoo, Michigan 49001 USA

CONTINUING MEDICAL EDUCATION

(Continued from Page 289)

September 5-6—**Recent Advances in Obesity.** Seattle. Wednesday-Thursday. Health Sciences Center. Contact: U/W.

September 6-7—**Symposium on Breast Disease.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

September 7-8—**Nutrition and Bone Metabolism.** Seattle. Friday-Saturday. Health Sciences Center. Contact: U/W.

September 8-15—(ALBERTA) **Neurosurgery of Pain.** Banff. Saturday-Saturday. Banff Park Lodge. Contact: U/W.

September 10-14—**Advances in Family Practice.** Seattle. Monday-Friday. Health Sciences Center. Contact: U/W.

September 10-14—**Advances in Family Practice With ACLS Pathway.** Seattle. Monday-Friday. Health Sciences Center. Contact: U/W.

September 11-12—**Conference on Homeostatic Functions in the Elderly.** Sheraton St. Louis Hotel, St. Louis, MO. Contact: Sharon Smith, Conference Secretary, Geriatric Center (111G-JB), VA Medical Center, St. Louis, MO 63125. (314) 894-4659.

September 12-14—**Dermatologic Therapeutic Hotline.** Orcas Island. Wednesday-Friday. Rosario Resort. Contact: Paul H. Jacobs, MD, Department of Dermatology, Stanford University Medical Center, Stanford, CA 94305. (415) 497-7854.

September 13-16—**Washington State Medical Association Annual Meeting.** Seattle. Thursday-Sunday. Westin Hotel. Contact: Patti Smith, WSMA, 2033 Sixth Avenue, #900, Seattle 98121. (206) 623-4801.

September 15-16—**Skin Surgery.** Seattle. Saturday-Sunday. U/W Health Sciences. Contact: U/W.

September 16-23—(PUERTO VALLARTA, MEXICO) **Management of Pain.** One week. Camino Real. Contact: U/W.

September 26—**Advances in Lab Medicine.** Seattle. Wednesday. Health Sciences Center. Contact: U/W.

October 3-5—**Molecular Medicine.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

October 5—**Practical Pulmonary Function.** Seattle. Friday. Contact: VMMC.

October 12—**Frontiers in Eye Care for the Allied Professional.** Seattle. Friday. Contact: VMMC.

October 12-13—**Neurology Update.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

October 13—**Radiology Northwest.** Saturday. U/W Health Sciences Center. Contact: U/W.

October 19—**Annual Cancer Conference: Early Screening and Detection.** Seattle. Friday. Contact: VMMC.

October 20—**Medical Alumni Day.** Seattle. U/W Health Sciences. Contact: U/W.

October 25-26—**Advances in Internal Medicine.** Thursday-Friday. U/W Health Sciences Center. Contact: U/W.

November 1-2—**Washington Chapter—American College of Emergency Physicians.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, WACEP, 2033 Sixth Avenue, #900, Seattle 98121. (206) 623-4801.

November 1-2—**Drug Therapy.** Seattle. Thursday-Friday. Westin. Contact: U/W.

November 2-3—**Asbestos Related Lung Disease.** Seattle. Friday-Saturday. Contact: Ed Oshiro, Medical Education, Group Health Cooperative, 201 16th Ave E, Seattle 98112. (206) 326-7348.

November 8-9—**Alzheimers.** Seattle. Thursday-Friday. Westin. Contact: U/W.

November 9—**GI Update.** Seattle. Friday. Contact: VMMC.

November 15-16—**Death Investigation.** Seattle. Thursday-Friday. Westin. Contact: U/W.

November 17-24—(HAWAII) **Medicine and Society in History.** One week. Inter-Continental Maui, Maui. Contact: U/W.

November 29-30—**Organ Failure and Organ Transplantation.** Seattle. Thursday-Friday. Westin. Contact: U/W.

December 1—**Medicine for Attorneys.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

December 6-7—**Aging and Elderly.** Seattle. Thursday-Friday. Westin. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Friday. Contact: VMMC.

December 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Westin. Contact: U/W.

December 15—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

January 11—**Treatable Hepato-Biliary Disease.** Seattle. Friday. Contact: VMMC.

January 24-26—**Annual President's Meeting—Modern Ophthalmic Technology.** Washington State Academy of Ophthalmology at Seattle. Thursday-Saturday. Westin. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

January 31-February 1—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin. Contact: U/W.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 16—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

March 2—**Nutrition of Hospitalized Patients.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

WYOMING

September 9-15—**Effective Management of Common Sports Injuries: An EPIC Medical Expedition.** Bicycle touring through Yellowstone and Grand Teton National Parks. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: June 8-12, 1984, Valdez Convention Center.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and Country, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 20-22, 1984, Mark Marriott, Vail.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: November 9-11, 1984, Kauai Surf Hotel, Kauai.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1985—date and place to be announced.

Montana Medical Association—2012 11th Ave., Sulte 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: November 2-4, 1984, OMA Headquarters, Portland (House of Delegates).

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1985—date and place to be announced.

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Improving the outlook... in mixed depression and anxiety

A rational approach, combining

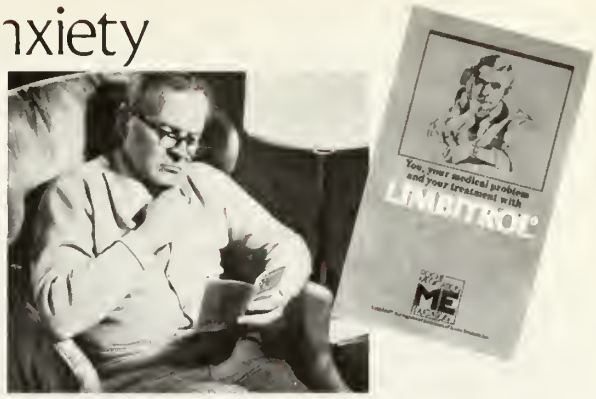
- The standard antidepressant: amitriptyline
- The proven anxiolytic: Librium® (chlordiazepoxide HCl/Roche)Ⓥ

Marked improvement often occurs as early as the first week.

Headache, insomnia or GI upsets associated with mixed depression and anxiety often respond quickly.

Feeling better, patients feel encouraged to stay the course—therefore, fewer dropouts due to side effects: $p < 0.006$ compared to amitriptyline.* Patients should be cautioned about the combined effects of Limbitrol with alcohol and other CNS depressants, and about activities requiring complete mental alertness such as operating machinery or driving a car.

*Feighner JP: *Psychopharmacology* 61 217-225, Mar 22, 1979.



A Roche Medication Education Booklet—
"You, your medical problem and your treatment with Limbitrol."

Valuable adjunct to dual therapy with Limbitrol:

Because an informed patient is more responsive...

This easy-to-read brochure explains the rationale of dual therapy with Limbitrol and encourages patient compliance. To obtain a complimentary supply, please contact your Roche representative.

In moderate depression and anxiety

Limbitrol®Ⓥ

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

LIMBITROL® Tablets Ⓥ
Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra pyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement; galactorrhea and minor menstrual irregularities in the female; elevation and lowering of blood sugar levels; and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25: initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5: initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

ROCHE®
ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

CLEARING: BOTH THE DEPRESSION AND THE ANXIETY...

ROCHE

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

Please see summary of product information on reverse side.

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The Western Journal of Medicine

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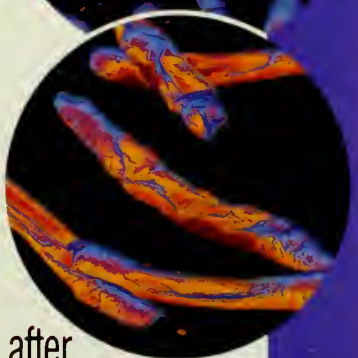
Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Strong on results.

before

Color-enhanced scanning electron micrograph shows *E. coli* 736 culture growing on Adams and Roe agar.



after

E. coli 736 culture after 24-hour incubation with Bactrim (trimethoprim and sulfamethoxazole/Roche) at 5×MIC. Note distorted shape of destroyed bacteria.

Simple to take.

ROCHE®

In recurrent urinary tract infections

- **Clears the urinary tract of a wide range of susceptible pathogens**
- **Rapidly relieves symptoms of urgency and dysuria**
- **Destroys potential pathogens that colonize the vaginal area**

Bactericidal against *E. coli* and other uropathogens *in vitro*

Bactrim demonstrates bactericidal action against major uropathogens *in vitro*. *E. coli*, *Klebsiella pneumoniae* and *Enterobacter* were all rapidly destroyed by Bactrim at 5× MIC levels—and these levels are usually greatly exceeded in the urine after a standard dosage of Bactrim DS.[1] However, *in vitro* activity does not necessarily correlate with clinical results.

Unsurpassed efficacy in clinical practice

In chronic or recurrent urinary tract infections, Bactrim is highly effective[2] and has been repeatedly recommended for its strong results,[3] its site-to-source action (in urinary tract, vagina and bowel)[4] and its ability to penetrate the renal parenchyma in chronic pyelonephritis.[5] Clinicians often prefer Bactrim as treatment for the entire course of therapy when the organism is known to be susceptible,[6] and as first-line therapy in recurrent urinary tract infections.[7]

Effective and economical *b.i.d.* therapy

Just one Bactrim DS tablet *b.i.d.* for 10 to 14 days provides effective, economical therapy for recurrent urinary tract infections.

Bactrim is indicated for the treatment of recurrent urinary tract infections due to susceptible strains of *E. coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris* and *Proteus morganii*. However, it is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single antimicrobial agent rather than the combination.

Maintain adequate fluid intake during therapy. Bactrim is contraindicated in pregnancy at term, during lactation, in infants under two months of age and in documented megaloblastic anemia due to folate deficiency.

Bactrim™ DS

(trimethoprim and sulfamethoxazole/Roche)

B.I.D. for enhanced compliance.

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Please see summary of product information on the following page.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Wormser GP, Keusch GT, Heel RC: *Drugs 24*:459-518, Dec 1982. 3. Ronald AR: *Clin Ther 3*:176-189, 1980. 4. Rubin RH, Swartz MN: *N Engl J Med 303*:426-432, Aug 21, 1980. 5. Cunha BA: *Postgrad Med 70*(6):149-156, Dec 1981. 6. Neu HC: *Infectious Diseases 10*(6):4, 19, Jun 1980. 7. Jones SR: *Ration Drug Ther 13*(11):1-5, Nov 1979.

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults. Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment. Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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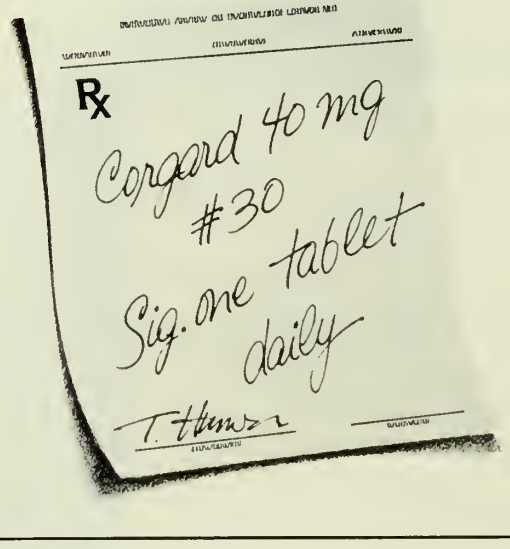

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WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal–Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)– PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery–Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function–Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions–Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy–In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers–It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**– Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis. **Hematologic**–agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

SQUIBB®
Innovators in cardiovascular medicine

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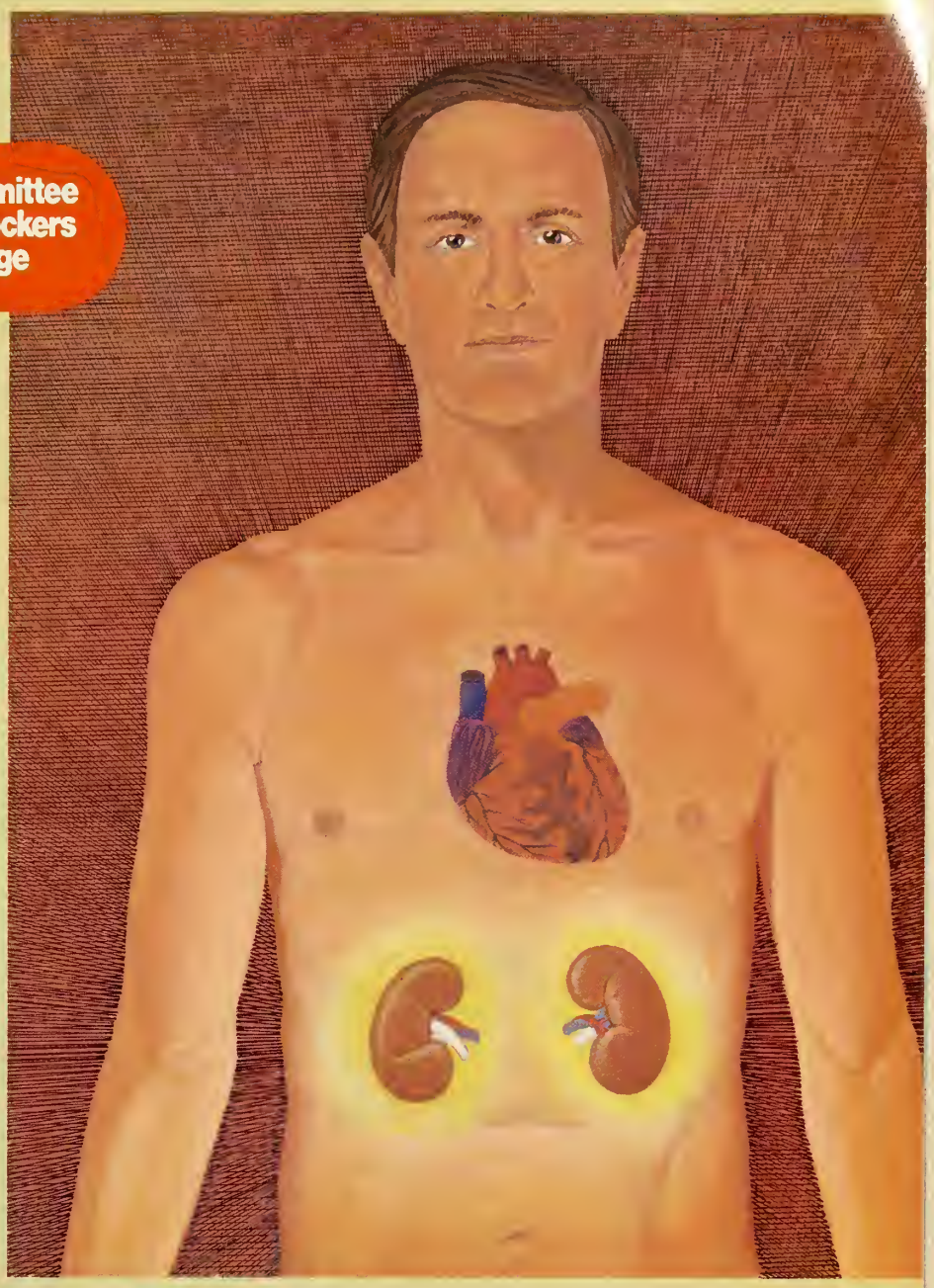
514-519

Issued: June 1984

The Joint National Committee now advocates beta-blockers for broad Step-1 usage

IN HYPERTENSION
CORGARD®
(nadolol tablets)

BLOCKS BETA RECEPTORS IN THE HEART WHILE APPARENTLY PRESERVING RENAL BLOOD FLOW



Effect on kidney

"...investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function."[1]

"...the majority of investigators utilizing propranolol have reported decrements in RPF [renal plasma flow] and GFR [glomerular filtration rate]..."[1]

CORGARD® (nadolol tablets) should be used with caution in patients with impaired renal function.

Reference: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Mineral Electrolyte Metab 8: 237-254, 1982.

SQUIBB®
Innovators in cardiovascular medicine

TAKE THE ADVANTAGE TO HEART

Please see the adjacent page of this advertisement for brief summary.

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ALLERGY AND IMMUNOLOGY

October 4-6—**Allergy/Immunology.** UCSF. Thursday-Saturday.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** UCSF at Hotel Meridien, San Francisco. Monday-Thursday. $375.

October 20—**Allergy Update—A Clinical Symposium.** Allergy Foundation of Northern California, Allergy Association of Northern California and the California Society of Allergy at Holiday Inn Union Square, San Francisco. Saturday. Contact: Dr. Chester Trossman, 500 E. Remington Dr., Sunnyvale 94087. (408) 730-0812.

October 24-28—**American Association for Clinical Immunology and Allergy Meeting** at San Diego. Wednesday-Sunday. Contact: Howard S. Silber, Exec. Dir., PO Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

October 25-28—**Allergy, Immunology and Infectious Disease.** Symposium Maui, Inc. and Hawaii Chapter American Academy of Family Physicians at Maui Marriott, Kaanapali, Maui. Thursday-Sunday. 18 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., PO Box 10185, Lahaina, Maui, HI 96761. (808) 661-8032.

December 27-29—**Allergy and Asthma.** Hawaii Medical Association and Hawaii AAFP at Royal Lahaina Resort, Maui. Thursday-Saturday. $275. 13.5 hrs. Contact: Joe Harrison, MD, Dir., PO Box 10185, Lahaina, Maui 96761.

ANESTHESIOLOGY

September 28-30—**Anesthesia Practice 1984.** Anesthesiology Education Foundation at Monterey. Friday-Sunday. 10½ hrs. Contact: AEF, PO Box 24230, Federal Bldg., Los Angeles 90024.

October 20—**Annual Anesthesiology Symposium.** Kaiser Permanente Southern California Medical Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

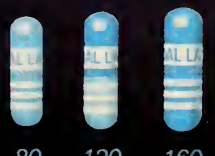
USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

Just once each day...
First-step blood pressure control with optimal simplicity
Benefits diuretics cannot offer... Once-daily INDERAL LA (propranolol hydrochloride) with its smooth 24-hour control of blood pressure provides a high degree of patient acceptance without potassium problems, plus the cardiovascular benefits of the world's leading beta blocker.
Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



80 mg 120 mg 160 mg

The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

Just once each day for initial therapy in hypertension.

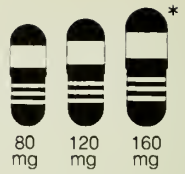
Ayerst

Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL* LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure, intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

Just once each day for initial therapy...

(Continued from Page 305)

CANCER

October 18-20—**8th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. $300. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

December 7-8—**2nd Annual Recent Advances in Occupational Cancer Focus on Prevention.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $150.

CARDIOLOGY

September 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Meridien Hotel, San Francisco. Thursday-Saturday.

October 7-10—**Cardiology Course**. UCSF at Yosemite. Sunday-Wednesday.

October 11-13—**Cardiology Update—1984.** ACC at Hyatt Del Monte Hotel, Monterey. Thursday-Saturday.

October 15-19—**Pulmonary Medicine Review 1984.** USC. Monday-Friday. $450.

October 19-21—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center and Medical Education Resources at Islandia Hyatt, San Diego. Friday-Sunday. 13 hrs. Contact: Med. Ed. Resources, 5808 So. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

October 26-28—**ECG Interpretation, Arrythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at San Francisco. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 2-4—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center and Medical Education Resources, 5808 So. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

November 2-4—**The Diagnosis and Management of the Acute Myocardial Infarction.** International Medical Education Corporation at Newporter Inn, Newport Beach. Friday-Sunday. Contact: Beverly Jacobsen. (800) 525-8651.

November 9-10—**Cardiology Update 1984.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. Contact: Lore Kahane, C-SMC, PO Box 4870, Los Angeles 90048. (213) 855-5547.

November 30-December 2—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress & Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 30-December 2—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact Beverly Jacobsen, 64 Inverness Dr. E., Englewood, CO 89112. (800) 525-8651.

December 7-9—**Cardiovascular Disease: Non-Invasive Diagnostic Method (Stress and Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at San Diego. 13 hrs. Friday-Sunday. Contact: IMEC, 64 Inverness Drive E., Englewood, CO 80112. (800) 525-8651.

December 7-9—**Advances in Heart Disease 1984.** American College of Cardiology at Hyatt Regency Hotel, San Francisco. Contact: ACC, 911 Old Georgetown Rd, Bethesda, MD 20814.

EMERGENCY MEDICINE

September 17-21—**Postgraduate Institute for E.R. Physicians, Symposium I.** UCSD at InterContinental Hotel, San Diego. Monday-Friday. 36 hrs.

September 28-29—**Advanced Trauma Life Support Provider Course.** Emergency Shock Trauma Institute, Mercy Hospital at San Diego. Friday-Saturday. 16 hrs. $475. Contact: Emergency Shock Trauma Institute, Mercy Hospital, 4077 5th Ave., San Diego 92103. (619) 294-8111.

October 13—**Emergency Medicine Oral Boards Part II.** Highland General Hospital at Hyatt Regency Hotel, Oakland. Saturday. $495. Contact: Robert H. Dailey. (415) 534-8055, Ext. 207.

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LINN GOLDBERG, MD, and DIANE L. ELLIOT, MD

From the Division of General Internal Medicine, Department of Medicine, The Oregon Health Sciences University, Portland.

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MICHAEL GILFIX, JD, and THOMAS A. RAFFIN, MD

Dr Gilfix is the former Director of Senior Adults Legal Assistance of Santa Clara County, California, and now specializes in medicolegal law in Palo Alto, California, and Dr Raffin is Assistant Chief of Medicine and Assistant Professor of Medicine (Respiratory), Stanford University Medical Center, Stanford, California.

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From the Department of Medicine, Good Samaritan Hospital and Medical Center, Portland.

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M. ROY SCHWARZ, MD

At the time this paper was written, Dr Schwarz was Dean of the University of Colorado School of Medicine. He now is Vice President for Medical Education and Science Policy, American Medical Association, Chicago.

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PETER RANK, JD, and DILEEP G. BAL, MD, MPH

Dr Rank is Director of the California Department of Health Services, and Dr Bal is Chief of the Adult Health Section, California Department of Health Services, Sacramento.

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★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: The Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

BALANCED CALCIUM CHANNEL BLOCKADE!

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

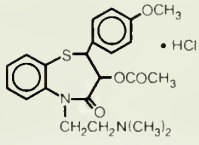
2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CAROIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CAROIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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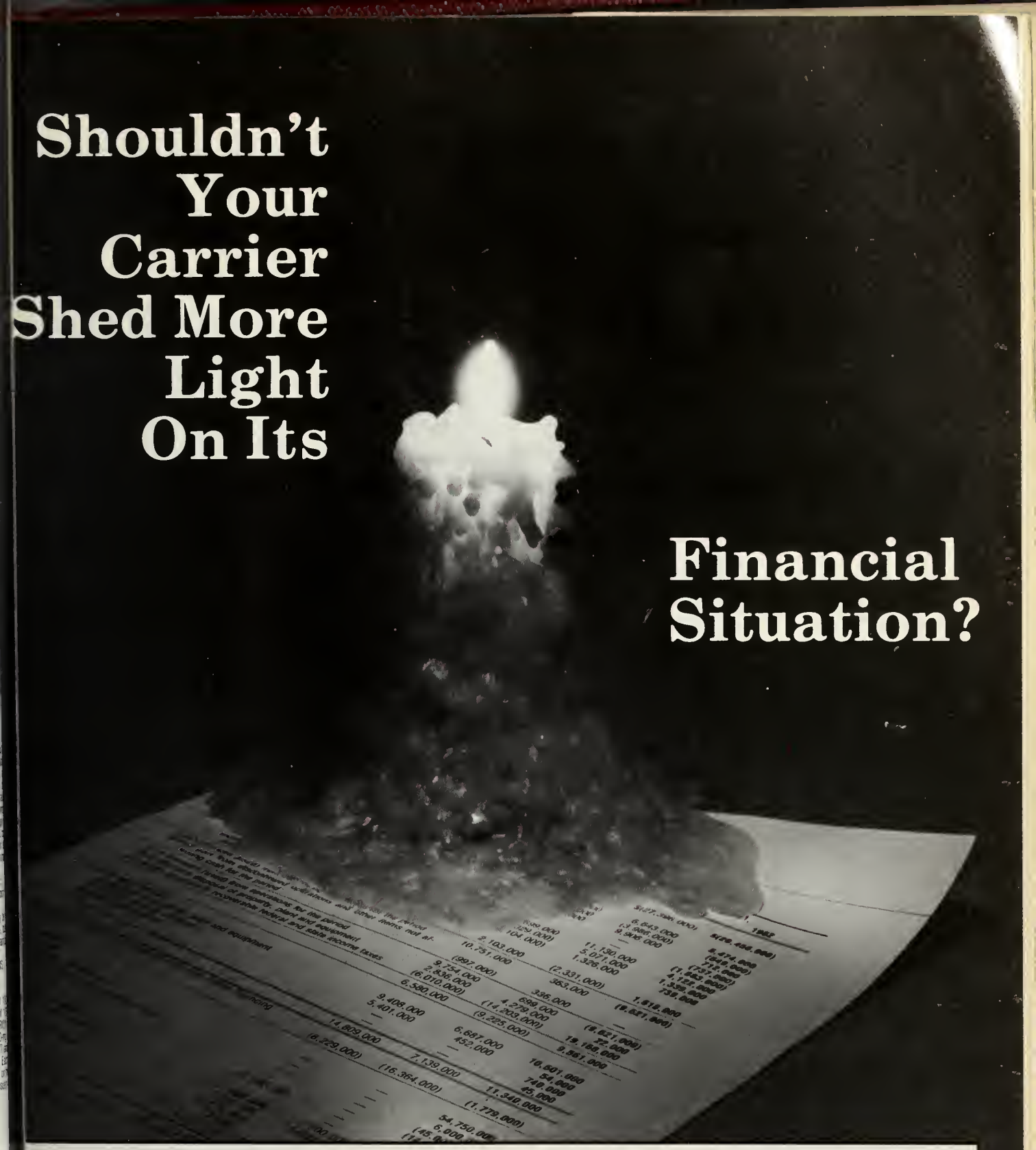

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ICA

The Preferred Underwriter

In clinical anxiety,

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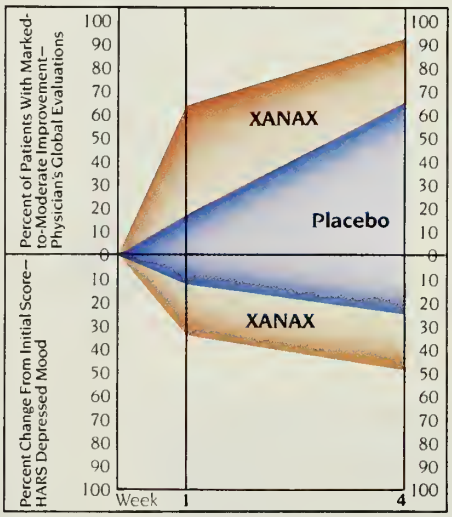
Kalamazoo, Michigan 49001 USA

depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

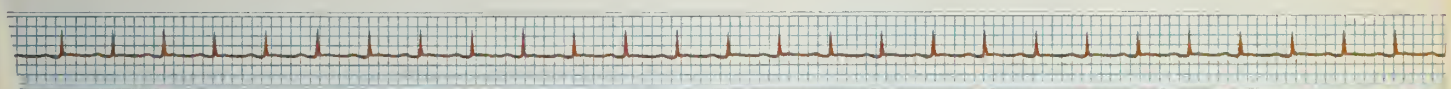
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).



A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy



- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file, The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets

alprazolam C-IV

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility.* No carcinogenic potential or impairment of fertility in rats. *Pregnancy* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery* No established use. *Nursing Mothers.* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use.* Safety and effectiveness in children below the age of 18 have not been established

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness

Central nervous system Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular. Tachycardia/palpitations, and hypotension.

Sensory Blurred vision

Musculoskeletal: Rigidity and tremor.

Cutaneous Dermatitis/allergy

Other side effects: Nasal congestion, weight gain, and weight loss

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

B-3-S

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CONTINUING MEDICAL EDUCATION

(Continued from Page 309)

October 29-30—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

October 29-November 2—**Intensive Care.** STAN at Rickey's Hyatt, Palo Alto. Monday-Friday.

October 31-November 2—**EMS Today.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 19 hrs.

November 12-16—**Postgraduate Institute for E.R. Physicians, Symposium III.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Friday.

December 2-7—**Kauai 1984 "Current Concepts in Emergency Care."** The Institute for Emergency Medical Education and the Washington Chapter of the American College of Emergency Physicians at Kauai Surf Hotel, Kauai. Sunday-Friday. 25 hrs. Contact: Georgine Fleck, Kailani World Travel, 4192 Meridian Avenue, Bellingham, WA 98277-9951. (800) 426-2561.

December 10-14—**Postgraduate Institute for E. R. Physicians, Symposium II.** UCSD at La Jolla Village Inn, La Jolla. Monday-Friday. (619) 452-3940.

INTERNAL MEDICINE

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 19—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wednesday. Contact: Charles R. Beeson, MD, Assoc. Chief of Staff for Ed., VA Medical Center, 16111 Plummer St., Sepulveda 91343. (818) 891-2374.

September 19—**Controversial Problems of the Pancreas.** Cedars-Sinai Medical Center at Los Angeles. Wednesday. Contact: Lore Kahane, Cedars-Sinai Medical Center, PO Box 48750, Room 2049, Los Angeles 90048. (213) 855-5547.

CONTINUING MEDICAL EDUCATION

September 21-22—**29th Annual Internal Medicine Symposium.** Kaiser Permanente Southern California Medical Group at Disneyland Hotel, Anaheim. Friday-Saturday. $150. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 1-5—**Present Concepts in Internal Medicine.** American College of Physicians at San Francisco. Monday-Friday. Contact: ACP Headquarters, (215) 243-1200.

October 15-18—**Rheumatology, Allergy, Clinical Immunology: An Advanced Course.** See Allergy and Immunology, October 15-18.

October 17—**Diabetes—1984.** The Hospital of the Good Samaritan at Hyatt Regency Hotel Los Angeles, Los Angeles. Wednesday. Contact: Dolores Gay, Coordinator of Symposia, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

October 19-21—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** Continuing Medical Education Associates at Vacation Village Hotel, San Diego. Friday-Sunday. Contact: Jackie Shiller, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

November 2-3—**Thyroid/Diabetes Workshop.** UCSF. Friday-Saturday.

November 2-4—**Practical Endocrinology: Workshop in Thyroid and Diabetes.** UCSF at Claremont Resort Hotel, Berkeley. Friday-Sunday. Reg. Info.: 666-5808. Program Info.: 666-4251.

November 10—**Infectious Disease.** UCD at Holiday Inn Holidome, Sacramento. Saturday.

November 10—**Pulmonary Medicine.** UCSF at Fresno. Saturday. Contact: Sharon Balestra (209) 225-6100 Ext. 562 or 207.

November 14—**Rheumatology—X-Ray of the Joints.** LLU. Wednesday.

November 16-18—**Pulmonary Medicine and Office Spirometry for P.C. Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday.

December 7-8—**Rheumatology for the Clinician.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday.

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OBSTETRICS AND GYNECOLOGY

September 28-29—**Outpatient Gynecology in the 1980's Progress and Expectations.** Center for Health Education at Long Beach. Friday-Saturday. 10 hrs. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 6—**Clinical Ultrasound—OB/GYN Update.** Sacramento Radiology Research and Education Foundation and the Northern California Radiology Society. Saturday. $75. Contact: J. P. McGahan, MD, Program Director, Sacramento Radiology Research and Education Foundation, PO Box 19184, Sacramento 95819.

October 7-9—**The Neural and Metabolic Bases of Feeding.** See Pediatrics, October 7-9.

October 10-22—**22nd Hysteroscopy Course.** The Hospital of the Good Samaritan, Los Angeles. $150. 1½ weeks. Contact: Janie Sternal, Dir. CME, Hospital of the Good Samaritan, 616 So. Witmer St., Los Angeles 90017. (213) 977-2335.

October 22-27—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** UCI. Monday-Saturday.

December 13-15—**Gynecologic Surgery.** The American College of OB/GYN at Hyatt Regency Hotel, Los Angeles. Thursday-Saturday. Contact: ACOG, Patience A. Schenck, 600 Maryland Avenue, SW, Washington, DC 20024. (202) 638-5577.

OPHTHALMOLOGY

October 10—**Ophthalmology-Therapeutic Decision re: Glaucoma, Retinopathy and Cataracts.** LLU. Wednesday.

October 11-13—**Cosmetic Blepharoplasty Workshop.** JSEI. Thursday-Saturday.

October 20—**Update for Nonophthalmologists: Ocular Diseases of Aging.** JSEI. Saturday.

November 30-December 1—**Phacoemulsification, Extracapsular Cataract Surgery & Intraocular Lenses.** Jules Stein Eye Institute at Los Angeles. Friday-Saturday.

December 7-8—**Glaucoma Management: The State of the Art.** UCSF at Hyatt Regency Hotel, San Francisco. Friday-Saturday.

December 8—**Ophthalmology Association Clinical Meeting.** Jules Stein Eye Institute at Los Angeles. 5 hrs. Saturday. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

PATHOLOGY

November 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday.

PEDIATRICS

October 3-4—**41st Annual Brenneman Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Red Lion Motor Inn, Sacramento. Sunday-Tuesday.

October 20-27—**9th Annual Pediatrics for the Practitioner.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 26-27—**Adolescents Inside and Out.** Children's Hospital Medical Center of Northern California and California Chapter 1 of the American Academy of Pediatrics at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes-Dodd, Medical Staff Office, Children's Hospital Medical Center, 51st and Grove St., Oakland 94609. (415) 428-3334.

November 10—**Physiologic Review of the Fetus and Newborn.** UCSD at Bahia Hotel, San Diego. Thursday-Saturday.

November 16-19—**Clinical Pediatrics.** California Chapters 1, 2 & 3 American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

December 3—**Issues in Perinatal Care.** UCSF. Monday.

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CONTINUING MEDICAL EDUCATION

December 6-9—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Rancho Mirage. 14 hrs. Thursday-Sunday.

PSYCHIATRY

November 9-11—**30th Annual Group Therapy Symposium.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

RADIOLOGY

September 17-20—**American College of Radiology Meeting** at Century Plaza Hotel, Los Angeles. Monday-Thursday. Contact: ACR, 20 N. Wacker Dr., Chicago 60606. (312) 236-4963.

October 13—**11th Annual Radiology Symposium.** Kaiser Permanente Southern California Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 13-21—**9th Annual International Body Imaging Conference.** West Park Hospital at Royal Lahaina Hotel, Maui. One week. 28 hrs. $425. Contact: Conference Sec., 9th Annual Body Imaging Conf., Dept. of Radiology, West Park Hospital, 22141 Roscoe Blvd., Canoga Park 91304. (818) 340-0580, ext. 280.

October 19-21—**Duplex Scanning.** Institute for Medical Studies at Holiday Inn Fisherman's Wharf, San Francisco. Friday-Sunday. Contact: Kim Stroich, IMS, 30131 Town Center Drive, Ste. 215, Laguna Niguel 92677. (714) 832-2650 or 495-4499.

October 22-26—**9th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Monday-Friday.

November 5-9—**Diagnostic Radiology Seminar.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday.

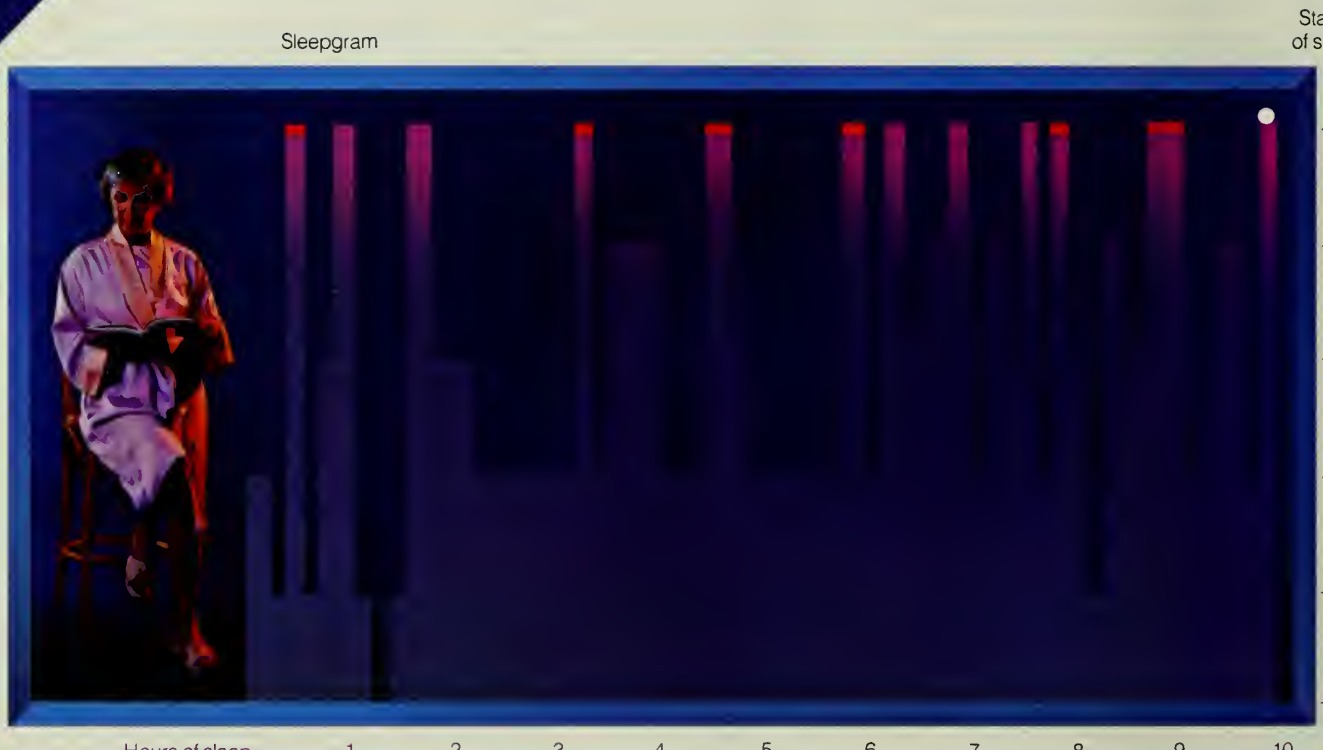
November 14—**Rheumatology—X-ray of the Joints.** LLU. Wednesday.

December 8—**Gastrointestinal Radiology.** Cedars-Sinai Medical Center at Los Angeles. Saturday. Contact: Lore Kahane, PO Box 48750, Room 2049, Los Angeles 90048. (213) 855-5547.

(Continued on Page 410)

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

= objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

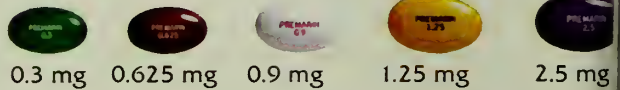
Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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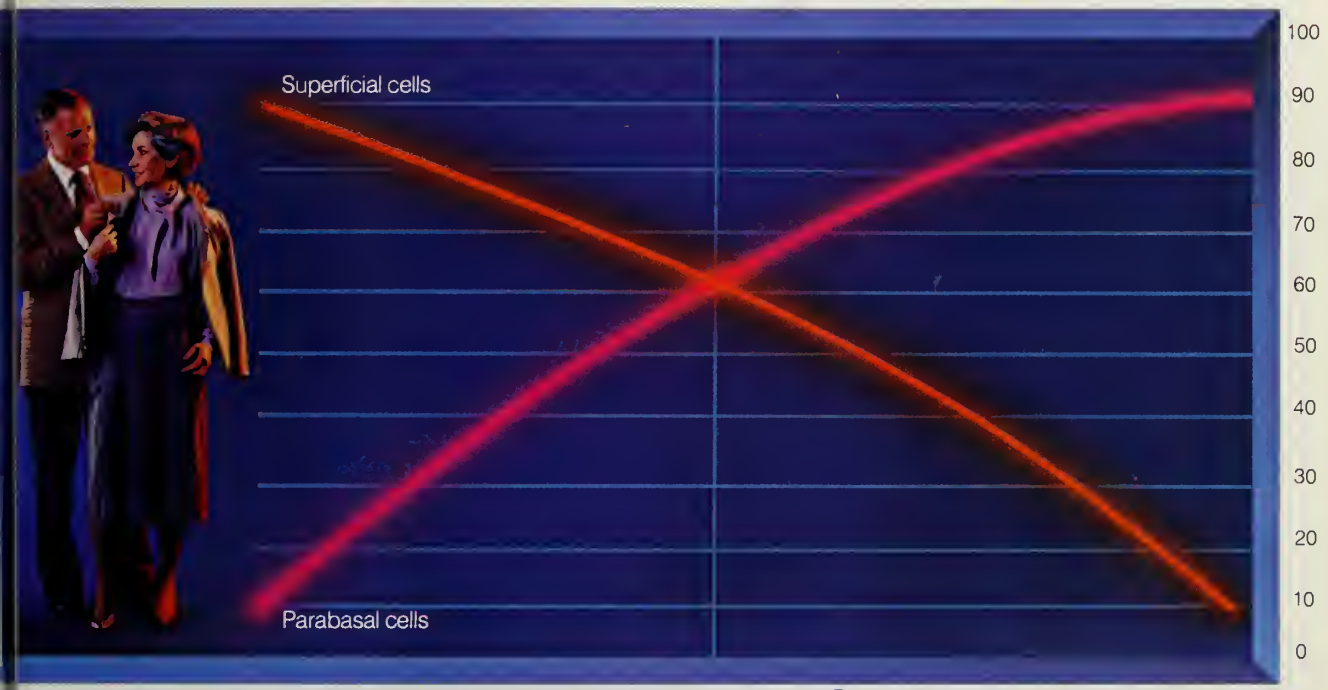
THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

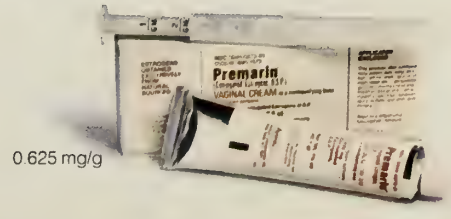
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

FOR ATROPHIC VAGINITIS

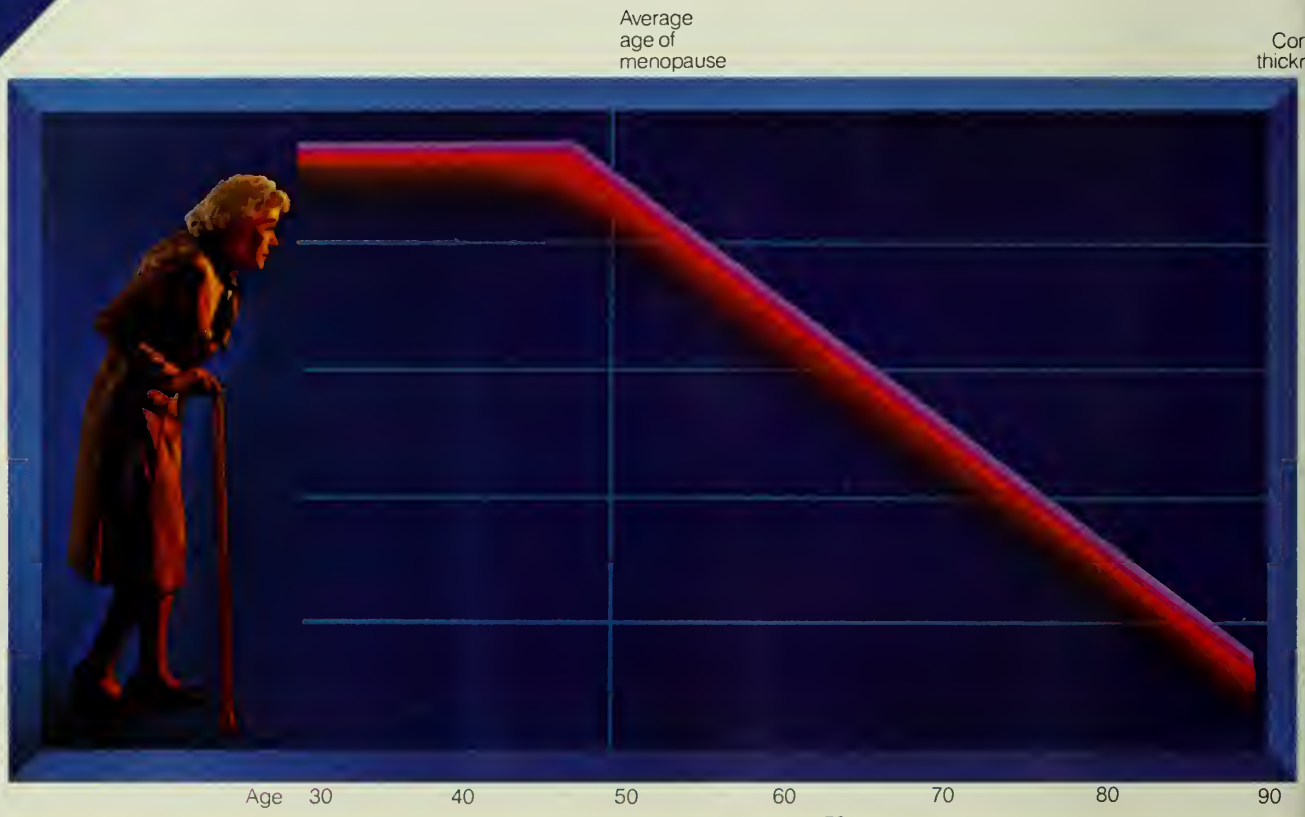
PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/g

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[5]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 n

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*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream. No. 872. Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **8934/984**

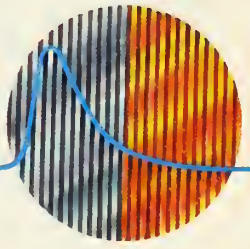
REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al. Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al. Estrogen replacement therapy. Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull*, June 1983, pp 1-5. 4. Ayers LJ. The maturation index. A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G. Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ. Age, estrogen, and bone density. *Clin Obstet Gynecol* 1981;24:203-218. 7. Gordan GS, Picchi J, Roof BS, et al. Postmenopausal osteoporosis. *Am Fam Physician* 1973;8:74-83. 8. US Bureau of the Census. *Statistical Abstract of the United States* 1982-83, ed. 103. Washington, DC, US Dept of Commerce, 1982, p 25. 9. Mallette LE. Osteoporosis: Approaching treatment with optimism. *Postgrad Med* 1982;72:271-278.

SAMPLE
EXCERPT

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

Halcion® 0.25 mg Tablets
triazolam (IV)

Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion
triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

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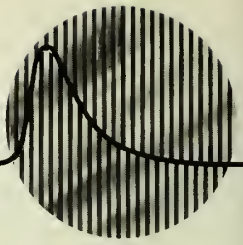
Halcion Tablets
triazolam (IV)



Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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It Pays to Save Potassium
K+
Potassium-Sparing
DYAZIDE®
Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.
In Hypertension*...When You Need to Conserve K+
Serum K+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contreindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Wernings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietery intake of potessium is merkedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therepy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without e history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, egranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide, dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

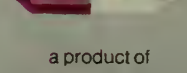
Thiazides may add to or potenliate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal reletionship has not been established.

Supplied: 'Dyazide' is supplied es a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (inlended for institutionel use only); in Patient-Pak™ unit-of-use bottles of 100.

The unique red and white Dyazide* capsule: Your assurance of SK&F quality.



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Brain Infarction and Hemorrhage in Young and Middle-aged Adults

JOSEPH R. LACY, MD; CHRISTOPHER M. FILLEY, MD; MICHAEL P. EARNEST, MD, *and* NEILL R. GRAFF-RADFORD, MB, BCh, MRCP (UK), *Denver*

Of 131 young (17 to 44 years) and middle-aged (45 to 55 years) adults who had brain infarction or hemorrhage, the most common etiologic factors were rheumatic heart disease, migraine and oral contraceptive use among the younger group. In contrast, atherosclerotic, hypertensive and diabetes-associated cerebrovascular diseases were the most common causes in the middle-aged group. Patients who have a stroke before age 45 should have prompt, complete laboratory and radiologic testing to define a possible treatable cause.

(Lacy JR, Filley CM, Earnest MP, et al: Brain infarction and hemorrhage in young and middle-aged adults. West J Med 1984 Sep; 141:329-334)

Cerebrovascular accidents (CVAs) are most prevalent among elderly persons and are uncommon in the young. In a large autopsy series, only 5% of cases of fatal CVA occurred in patients younger than 40 years,[1] and in an epidemiologic survey the incidence of CVA was only 25 per 100,000 young adults 35 to 45 years of age.[2] Etiologic factors in young persons who have cerebrovascular events are diverse and include rheumatic heart disease, migraine, oral contraceptive use, postpartum hypercoagulability and vasculitis.[3] Such causes stand in sharp contrast to those seen in older persons in whom atherosclerotic disease associated with hypertension and diabetes is the most common cause of CVA.

We present our experience with cases of brain infarction and hemorrhage in young and middle-aged adults from a large city hospital during a ten-year period (September 1, 1971, through August 31, 1981). This retrospective analysis was undertaken to determine (1) the causal factors among our group of young patients, and (2) whether or not the causes of CVA in the middle-aged persons were similar to those seen in younger patients or were the same as those encountered in the elderly.

Patients and Methods

We reviewed the records of patients between 17 and 55 years of age with brain infarction or hemorrhage who had been admitted to the adult neurology service at Denver General Hospital between 1971 and 1981. (All stroke cases presenting to the hospital without major medical complications had been admitted to the neurology service during the ten years reviewed. Patients younger than 17 years had been admitted to the pediatric service.) Cases were categorized as either infarction or hemorrhage according to the diagnosis listed in the patient records, as corroborated by radionuclide brain scan, computed tomographic (CT) scan, cranial arteriography or autopsy. A diagnosis of brain hemorrhage was accepted only if documented by CT scan or by an appropriate clinical syndrome plus mass effect shown on an angiogram. Patients with primary subarachnoid hemorrhage were excluded. The following two groups were established: group I included patients between 17 and 44 years of age; group II included patients between 45 and 55 years of age.

Records were reviewed with particular attention to the history of the present illness; a past history of cerebrovascular accident, hypertension, diabetes, migraine headaches, cardiac valvular disease, smoking, alcohol or other drug abuse, recent neck trauma and past or current use of oral contraceptives; a family history of cerebrovascular accidents, and findings on the general physical and neurologic examinations. Results of the following laboratory studies were sought: complete blood count, platelet count, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, VDRL, rheumatoid factor, antinuclear antibody, cho-

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Submitted, revised, January 30, 1984.
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ABBREVIATIONS USED IN TEXT

CT = computed tomography
CVA = cerebrovascular accident

lesterol, triglycerides, glucose levels, spinal fluid analysis, chest and skull x-ray films, electrocardiogram, Holter monitor, echocardiogram, radionuclide brain scan, head CT scan, cranial arteriogram and postmortem examination. Patients considered to have hypertension or diabetes included those with a documented history of either disorder and those who showed persistent hypertension (diastolic blood pressures greater than 95 mm of mercury) or glucose intolerance requiring treatment following hospital admission.

Based on the accumulated information, each patient was classified as having a probable, a possible or an unknown cause. For example, a patient with brain infarction who had hypertension and atherosclerotic disease by cranial arteriography was considered to have hypertensive cerebrovascular disease as a probable cause. In a similar patient who did not undergo arteriography, hypertensive cerebrovascular disease was the possible cause. A patient was considered to have atherosclerotic cerebrovascular disease only when significant atherosclerosis was found by arteriography but the patient had no past history or current evidence of hypertension or diabetes. Migraine was regarded as a probable cause when there was a history of complicated migraine and the CVA occurred during a typical migrainous episode; migraine was considered the possible cause when there was a strong history of migraine and the CVA occurred in the context of migraine headache but a previous history of similar complicated migraines could not be elicited. Oral contraceptive use and mitral valve prolapse were each regarded as possible causal factors.

TABLE 1.—*Type of Cerebrovascular Accident and Sex Distribution in 131 Patients*

	Group I (Aged 17-44 years)		Group II (Aged 45-55 years)	
	Infarction	*Hemorrhage*	*Infarction*	*Hemorrhage*
Men	22	8	38	8
Women	24	4	21	6
TOTALS	46	12	59	14

TABLE 2.—*Vascular Distribution of Brain Infarctions*

	Number of Patients	
Arteries/Veins	*Group I (Aged 17-44 years)*	*Group II (Aged 45-55 years)*
Left internal carotid	25	33
Right internal carotid	12	21
Vertebrobasilar	6	4
Multiple vessels	3	1
TOTALS	46	59

TABLE 3.—*Risk Factors for Cerebral Infarction and Hemorrhage*

	Patients		Statistical Probability of Difference*
Risk Factors	*Group I N = 58 Number (Percent)*	*Group II N = 73 Number (Percent)*	*P*
Hypertension	7 (12)	41 (56)	<.001
Diabetes	1 (2)	6 (8)	NSD
Cardiac valvular disease	6 (10)	5 (7)	NSD
Hyperlipidemia	....	2 (3)	NSD
Migraine	9 (16)	2 (3)	.009
Oral contraceptive use	7 (12)	....	.002
Intravenous drug abuse	2 (3)	....	NSD
Alcoholism	7 (12)	21 (29)	.021

NSD = no significant difference

*By chi-square test

Results

A total of 131 patients met the criteria for inclusion in the study. Of these, 58 were between 17 and 44 years of age (group I) and 73 were between 45 and 55 years old (group II). Brain infarctions were far more prevalent than hemorrhages, occurring in 80% of each group. The sex distribution of patients within each group is shown in Table 1. The ratio of men to women was about equal in group I patients with brain infarctions whereas in group II, the ratio of men to women who had infarctions was 1.8:1. The race distribution was the same in the two groups; overall, 52% were white, 29% were black, 18% were hispanic and 1% were North American Indians.

The vascular distribution of brain infarctions for patients from both groups is shown in Table 2. In each group, there was a preponderance of left carotid distribution events: 54% (25/46) in group I and 56% (33/59) in group II. In order of decreasing frequency, infarctions in the remaining patients occurred in the right carotid, vertebrobasilar and multiple vascular distributions. Also, the greatest number of intracranial hemorrhages occurred on the left. Combining the two groups, there was a total of 26 hemorrhages, of which 13 (50%) were in the left cerebral hemisphere, 8 (31%) were in the right cerebral hemisphere and 5 (19%) were in the brain stem or cerebellum.

The prevalence of certain risk factors for CVA among patients from the two groups is shown in Table 3. Of note, a history of hypertension was elicited in only 7 (12%) of 58 patients in group I, whereas 41 (56%) of the 73 in group II were known to have hypertension. Diabetes was present in only one (2%) patient in the former group and six (8%) in the latter. In group I, a history of cardiac valvular disease, of migraine and of oral contraceptive use was present in six (10%), nine (16%) and seven (12%) patients, respectively. In group II, only five (7%) patients had a history of cardiac valvular disease, two (3%) had a history of migraine and none were taking oral contraceptives. Statistically significant differences between

the older and younger groups were shown for hypertension, migraine, oral contraceptives and alcoholism.*

Routine laboratory studies, including a complete blood count, platelet count, prothrombin time, partial thromboplastin time, serum cholesterol and, less commonly, serum triglyceride levels, were done in the large majority of patients. Significant elevation of the hematocrit was found in one patient in each group. Otherwise, no consistent association was found between any laboratory abnormality and CVA in either group.

*Statistical analysis was done by Gary Knapp, MA.

TABLE 4.—*Frequency of Radiologic Tests*

Tests	Number of Patients: Group I N=58	Group II N=73
Echocardiogram	32	27
Nuclide brain scan	32	35
CT scan	28	40
Arteriogram	47	49

CT = computed tomography

TABLE 5.—*Possible and Probable Causes of Brain Infarction*

	Group I N=46	Group II N=59	Statistical Probability of Difference* P
Cardiac Disease			
Rheumatic heart disease	6	3	NSD
Prosthetic valve	..	1	....
Mitral valve prolapse	2	..	....
Myocardial infarction	1	1	....
Arrhythmia	..	1	....
TOTAL	9 (20%)	6 (10%)	NSD
Systemic Vascular Disease			
Hypertension	3	23	<.001
Hypertension and diabetes	1	5	....
Diabetes	..	2	....
Atherosclerosis	..	7	.016
Others†	1	1	....
TOTAL	5 (11%)	38 (67%)	<.001
Miscellaneous			
Migraine	6	..	.004
Oral contraceptive use	5	..	.009
Thrombotic thrombocytopenic purpura	2	..	....
Neck trauma	2	..	....
Iatrogenic	2	..	....
Multiple factors‡	3	1	....
Others§	7	1	....
TOTAL	27 (59%)	2 (3%)	
Unknown TOTAL	5 (11%)	13 (22%)	

NSD = no significant difference

*Chi-square test, used only if 5 cases or more in one group.
†Group I, vasculitis; group II, dissecting aneurysm.
‡Group I (1 patient each), oral contraceptives and migraine; oral contraceptives, migraine and mitral valve prolapse; hypertension and polycythemia; group II, hypertension, migraine, polycythemia and mitral valve prolapse.
§Group I (1 patient each), postpartum state; venous sinus thrombosis; neurosyphilis; carotid dissection; isolated intraluminal carotid thrombus of uncertain cause; radiation vasculitis; amphetamine vasculitis; group II, isolated intraluminal carotid thrombus of uncertain cause.

An electrocardiogram showed acute myocardial infarction in one person in each group. Echocardiography, radionuclide brain scan, CT scan and arteriography were done in most patients (Table 4).

In group I, five (11%) of the patients with brain infarction died, all of whom had postmortem examination, and six (50%) of those with intracranial hemorrhage died, of whom four had postmortem examination. In group II, seven (12%) of those with infarction and seven (50%) of those with hemorrhage died; four patients in each category had postmortem examinations.

Based on the foregoing, patients were classified as having a probable, a possible or an unknown cause for their infarction or hemorrhage. The etiologic categories of brain infarctions in the two groups are listed in Table 5. Cerebral embolism due to rheumatic valvular disease was the most frequent cause of cerebral infarction in the group of young patients (six cases). Oral contraceptive drug use was implicated as either the sole etiologic factor (five cases) or as one of multiple factors (two cases) in the group. Migrainous infarctions either probably occurred (three cases) or were presumed to have occurred (three cases) in a significant number of young patients as well. Instances of trauma-induced infarction (two cases), thrombotic thrombocytopenic purpura (two cases), infarction due to iatrogenic hypotension (two cases) and mitral valve prolapse (two cases) were seen less frequently. Single instances of a variety of other disorders were encountered including spontaneous carotid dissection, venous sinus thrombosis, neurosyphilis, myocardial infarction with mural thrombus and amphetamine vasculitis. Among the young patients, however, hypertension and diabetes-related vascular disease were uncommon (five cases).

Analysis of the differences showed the two groups were statistically different in that the younger had significantly more cases of rheumatic heart disease, migraine and the use of oral contraceptives. The older group had significantly more patients with hypertension and atherosclerosis (Table 5).

In group I patients with brain hemorrhages, arteriovenous malformations (three cases) were common while single instances of amphetamine vasculitis and acute bacterial endocarditis were also encountered. Only a fourth (three cases) of the hemorrhages in this group were hypertensive in origin.

A large portion of middle-aged patients with brain infarctions had either probable or possible hypertension or diabetes-related cerebrovascular disease, or both (26 cases); a significant number of this group also had documented atherosclerotic cerebrovascular disease with no known hypertension or diabetes (7 cases) (Table 5). Except for three instances of rheumatic heart disease with cerebral embolism, other causes of infarction were uncommon. Among the 14 middle-aged persons with brain hemorrhage, 11 cases were due to hypertensive vascular disease. Hypertension was significantly more prevalent in this group when compared

with group I ($\chi^2 = 7.462$, $P = .006$). For both groups, the causes for the infarctions or hemorrhages were unknown in only a small number of patients, probably because of the comprehensive workup of each case, including early angiography. Of note, among the patients with cerebral infarctions in group II who had no known cause, a large number were alcohol abusers (7 of 13 cases).

Discussion

Comparisons between studies of young persons with CVAs are made difficult by varying methodologies. Multiple sources of patients, a varying frequency of doing early angiography, different criteria for determining the cause and inclusion of different types of cerebrovascular events have led to many different conclusions concerning cause and outcome of CVA in young patients (Table 6).

In this study, we analyzed two groups with CVA, separating young and middle-aged persons, and compared etiologic factors between the two groups. In the middle-aged group, most brain infarctions and hemorrhages were related to either documented or presumed hypertensive or diabetic vascular disease (or both) or were due to atherosclerotic disease occurring without hypertension or diabetes. Our middle-aged patients were therefore etiologically similar to elderly patients in whom atherosclerotic disease is the usual cause of CVA. In contrast, hypertensive or diabetic (or both) cerebrovascular disease was an uncommon cause of brain infarction and hemorrhage among our young patients.

Although the differentiation of causes among young and middle-aged adults has not been specifically undertaken before, certain reviews have emphasized age-related etiologic differences among young persons with cerebrovascular accident. In a study of cerebral infarctions in young adults 16 to 49 years of age, Snyder and Ramirez-Lassepas reported that 29 of 63 (46%) had either documented or presumed atherosclerotic disease.[11] The youngest such patient was 36 years old and the mean age for this group with premature atherosclerosis was 47 years. In three other reviews where all patients were younger than 40 years, only 7% to

TABLE 6.—*Reviews of Stroke in Young and Middle-aged Adults*

Study	*Number of Cases*	*Age (Years)*	*Type of Stroke*	*Common Causes*	*Comments*
Hart et al, 1982[4]	100	<40	Cerebral infarction	Atherosclerosis, migraine and cardiac emboli 41%; contraceptives 17%; unknown 10%.	Early angiography produced high diagnostic yield.
Grindal et al, 1978[5]	58	15-40	Cerebral infarction	Unknown cause 45%; cardiac emboli 26%; occlusive extracranial disease 7%.	Hypertension prevalent but not defined as cause.
Hindfelt and Nilsson, 1977[6]	64	16-40	Brain infarction	Hypertension and diabetes 25%; migraine and contraceptive use 23%; cardiac disease 6%.	Found a seasonal variation, postulated role of viral infections.
Chopra and Probhakar, 1979[7]	251	<40	Infarct and hemorrhage	Hypertension and diabetes 8%; cardiac emboli 11%; puerperal 16%.	Series from India.
Marshall, 1979[8]	66	<40	Infarct and hemorrhage	Embolism 24% (only 8% from heart); hypertension 15%.	
Vignaendra et al, 1977[9]	13	<40	Cerebral infarction	Moyamoya disease 15%; other intracranial occlusions 23%.	From Malaysia.
Janaki et al, 1975[10]	26	<20	Stroke and TIA	Antecedent febrile illness 36.4%, more than half with pre-stroke seizures.	From India.
Snyder and Ramirez-Lassepas, 1981[11]	61	16-49	Cerebral infarction	Premature atherosclerosis 48%; contraceptives 11%.	Defined a high-risk group for subsequent stroke and death.
Louis and McDowell, 1967[12]	56	<50	Cerebral infarction	Hypertension, diabetes or "prediabetes" 75%; elevated lipids 10% to 12%.	Excluded embolic infarcts.
Wells and Timberger, 1961[13]	77	<50	Cerebral infarction	Hypertension 42%.	
Present study	131	≤55	Brain infarction	Hypertension 27%; cardiac emboli 14%; contraceptives 5%; unknown 17%.	Early angiography often done.
			Cerebral hemorrhage	Hypertension 54%; vascular malformation 12%.	

TIA = transient ischemic attack

12% had hypertensive or diabetic cerebrovascular disease.[5-7] In our series, the youngest patient to have atherosclerotic disease was 34 years of age. Atherosclerotic disease became more prevalent with advancing age and was the predominant cause of brain infarction and hemorrhage in persons older than 45 years. In considering the differential diagnosis of CVA in a young person, these findings emphasize that atherosclerotic cerebrovascular disease is rarely the cause before 35 years of age but that it becomes increasingly more common after age 35 and is the predominant cause of CVA after age 45 years.

The etiologic factors found among our group of young patients with infarction were most often rheumatic heart disease, migraine and the use of oral contraceptives. Other series of CVA in young persons have also reported a significant percentage of infarctions related to rheumatic heart disease.[5,7] However, except for one other series,[6] migraine-related infarctions have not been reported as commonly as in our study. Nevertheless, there is little doubt that migraine-induced vasospasm may result in cerebral infarction, especially in young persons.[14,15]

The role of oral contraceptive use as an etiologic factor in CVA remains somewhat controversial,[16-19] though there appears to be a clear increase in the risk of thrombotic CVAs among women older than 35 years taking these agents, particularly if they smoke.[19] In our series as in other reports,[6,8,11,20] a significant number of young women with CVA had no predisposing factors except oral contraceptive use. Two other women in this group were taking oral contraceptives and also suffered from migraine headaches or had documented mitral valve prolapse, factors that presumably increase the risk of CVA.

Mitral valve prolapse is a common valvular abnormality that is being increasingly recognized as a cause of embolic cerebral infarction among the young.[21-24] In our series and one other,[25] mitral valve prolapse was encountered only infrequently as a cause of infarction. This may not be a true reflection of the importance of this disorder, however, as our series included patients from a ten-year period during the early portion of which echocardiographic studies were not available.

Although alcohol abuse was not regarded separately as a causal factor in our review, the suggestion has been made in several studies that acute and chronic alcohol intoxication may be a precipitating factor in brain infarction,[26-30] particularly in the young.[26,28] Although the reason for this association is not entirely clear, recent studies have shown altered fibrinolytic activity[29,30] and other clotting abnormalities[30] with alcohol abuse. In our study, because of the nature of our hospital population, a significant percentage of persons in both our young (12%) and middle-aged (29%) groups were alcohol abusers. Perhaps more noteworthy was the finding that of our middle-aged patients with no cause for their CVAs, 7 of 13 (54%) had alcoholism; of these, two were intoxicated at the time of admission for their CVA. Our data, then, would lend support to the suggestion that alcohol abuse may increase the risk of CVA.

Other than hypertension and diabetes, factors that may increase the risk of CVA regardless of age include an elevated hematocrit,[31,32] smoking,[33] platelet and other clotting abnormalities[34,35] and lipid abnormalities.[36,37] Although the hematocrit was found to be significantly elevated in two instances in our series, we could not otherwise document that these factors were important among our patients. However, sophisticated studies of lipids and of platelet and other clotting factors were not done in most patients, and smoking histories were inadequately recorded.

A comprehensive diagnostic approach was taken to patients in both our groups but particularly in the young. Routine laboratory studies, x-ray films, electrocardiograms, spinal fluid analysis, cranial angiography, head CT scans and echocardiograms were done for all of our patients. As a result, the number of cases with an unknown cause was low: 22% in the middle-aged group and only 11% in the young group. Similar results were reported in other recent studies of CVA in the young.[4,38] With the application of newer diagnostic tools, the proportion of cases of CVA with no apparent cause should be reduced even further. Because the etiologic factors underlying this event are peculiar to that age group, and because many are potentially remediable, a comprehensive approach, including angiography, should be pursued for all young patients with a brain infarction or hemorrhage.

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Valued Outcomes in the Selection of a Contraceptive Method

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The perceptions and values of a sample of 106 women towards four contraceptive methods (oral contraceptives, intrauterine device, diaphragm and foam-and-condoms) were evaluated in the light of 24 identified issues of concern. The choice of a contraceptive method appears to represent a trade-off among negatively valued outcomes—the "best" method being least likely to incur undesirable consequences.

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For most women, choosing a birth control method is a difficult decision due to the variety of methods available and the degree of risk involved with their use. The few reported studies of contraceptive decision making[1-3] help to identify the sociodemographic characteristics of women who use a given contraceptive method. Comparatively little is known, however, about the important factors that influence a woman's choice of a specific method.

The process of selecting a birth control method involves two levels of decisions (Figure 1). First, a woman must decide whether she wishes contraception at all. Luker[4] has hypothesized a cost-benefit model whereby women weigh the relative value of pregnancy against the costs of contraception. When the value of pregnancy is low and the perceived likelihood of becoming pregnant without contraception is high, women begin to evaluate the contraceptive methods available to them. The second-order decision concerns her selection of a specific birth control method.

In considering alternative birth control methods logically, women must first identify the important issues of concern to them. Each such concern must then be weighed in terms of its relative value and its likelihood of occurrence when using each method being considered. That none of the existing methods is free from undesirable consequences means that difficult tradeoffs must inevitably be made.

To examine this complex process of contraceptive decision making, I first identified the concerns of women that influence their selection of a contraceptive method. Next, in light of these concerns, I explored the perceptions and values of women towards four contraceptive methods.

Patients and Methods

To identify the important concerns associated with selecting a contraceptive method, an open-ended questionnaire was distributed to 23 women in a private family practice and a family practice residency program. All had had some experience with contraception. A list of 93 factors or concerns was compiled from their responses. Seven women from the above sample were then asked to reduce this list by eliminating duplicated and vague statements. In all, 24 factors were finally selected. From these, a two-part questionnaire was developed and pretested (N = 8) for clarity and comprehensiveness.

The first part of the questionnaire solicited women's perceptions of the likelihood that each concern or outcome would result from using each of four contraceptive methods (diaphragm, pill, intrauterine device or foam-and-condoms) on a scale ranging from 1 (very unlikely) to 5 (very likely). In the second section they were asked to estimate the value of each concern on a scale of 1 (very bad) to 5 (very good) independent of contraceptive method. Also included were questions pertaining to the respondent's age, marital status, parity, contraception used (present and past) and her satisfaction with her current method.

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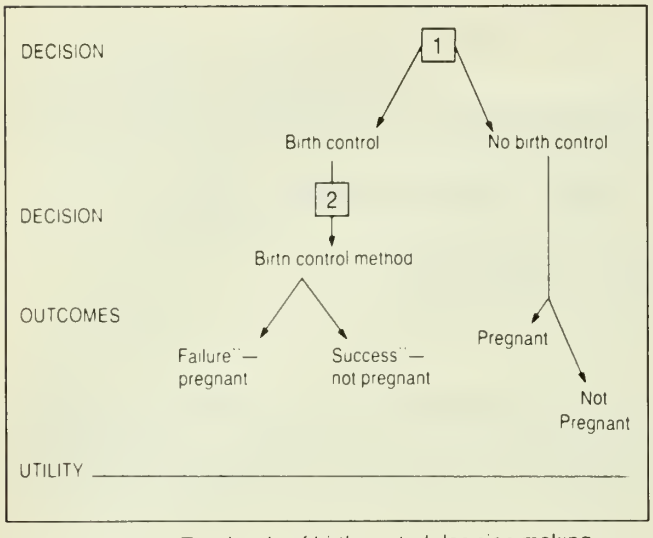

Figure 1.—Two levels of birth control decision making.

The questionnaire was then distributed to 106 women from a private family practice, a family practice residency program and a high school physical education class who represented a wide range of contraceptive experience. Selection of subjects was restricted to nonpregnant women aged 45 years and younger for whom contraception would be a relevant concern. As best as could be determined, none of the women had any special knowledge of birth control apart from that of the general population.

Results

In Table 1 are listed the demographic characteristics and contraceptive preferences of the sample population. Most were young, single and childless. The vast majority were using some form of contraception. Oral contraceptive users constituted about half of the sampled population, followed by those using a diaphragm. Most women appeared quite satisfied with their chosen method.

TABLE 1.—*Characteristics of Sample Population (N=106)*

	Number	*(Percent)*
Mean Age (years)	25.8	(range, 14-45)
Marital Status		
Single	64	(60.4)
Married	32	(30.2)
Separated/Divorced	10	(9.4)
Parity (mean, 0.51)		
0	77	(72.6)
1	12	(11.3)
2	11	(10.4)
3	4	(3.8)
4	2	(1.9)
Using Contraception		
Yes	90	(84.9)
No	16	(15.1)
Current Method*		
Pill	37	(43.0)
Diaphragm	18	(21.0)
Foam/condoms	11	(13.0)
Intrauterine device	6	(7.0)
Satisfied with Current Method*		
Very satisfied	35	(40.7)
Satisfied	33	(38.4)
Neither	10	(11.6)
Dissatisfied	7	(8.1)
Very dissatisfied	1	(1.2)

*Current methods not listed include tubal ligation (4) and other (11). Four persons did not respond to questions about current method and satisfaction with this method.

From the responses to the open-ended questionnaire, the concerns related to contraceptive decision making could be divided into nine groups. These included moral or religious beliefs towards contraception, the effects of a contraceptive method on sexual relations (spontaneity, enjoyment, frequency of intercourse), partner-related issues (acceptability, knowledge of method), convenience, side effects or health risks, anxiety or fear related to method usage, effects on present or future pregnancies, normative influences (advice of family, friends or personal physician) and a woman's sense of personal responsibility for birth control.

Four contraceptive methods were evaluated in light of these concerns (Table 2). All methods were perceived as unlikely to compromise a woman's moral or religious beliefs or influence the stability of her relationship. The diaphragm and foam-and-condoms were felt to be less convenient principally due to their interference with the spontaneity of intercourse. In addition, there was perceived a higher likelihood of pregnancy associated with these methods. The intrauterine device and oral contraceptives were felt to increase health risks and anxiety over these potential adverse effects.

While one might expect that a couple could not use the foam-and-condom method without complete knowledge of its use or that the diaphragm could be perceived to be used successfully without the "need to touch self" (Table 2, "convenience"), responses tended to follow a central bias, avoiding the extreme ends of the five-point scale. The trend of the responses does indicate, however, that the questions were adequately understood by the sampled population.

Table 3 shows how respondents valued the identified issues of concern independent of the contraceptive method used. Increased partner involvement and personal responsibility for birth control were positively valued. Negatively valued factors included a compromise of moral or religious beliefs; interference with sexual activity; inconvenient methods; increased fear or anxiety; increased risk of adverse side effects or pregnancy, and the advice of friends, family or physician against a method's use.

The values were then analyzed by age (Table 4), marital status (Table 5) and parity (Table 6) of respondents. Women aged 20 years and younger tended to place less importance on adverse side effects or increased fear related to the use of any contraceptive. Pregnancy was more negatively valued by single, nonparous women. While other findings were not statistically significant, several interesting trends were noted. Moral or religious concerns, impact on sexuality and greater health risks with concomitant fear or anxiety

TABLE 2.—*Perceptions Towards Selected Contraceptive Methods*

Consideration	Mean Scores of Respondents*			
	IUD	Pill	Diaphragm	Foam/Condoms
Compromise moral/religious beliefs	1.9	1.9	1.8	1.7
Effects on sexual relationship				
Less enjoyable sex	2.1	1.4	3.1	3.6
Interrupts spontaneity	1.6	1.2	3.7	4.1
Partner-related issues				
Unacceptable to partner	2.1	1.7	2.2	3.1
Stabilize relationship	2.5	2.6	2.2	2.0
Partner knows of method	2.9	2.6	4.2	4.7
Convenience				
Easy to use	3.6	4.3	2.1	1.9
Must remember to use method	1.6	4.2	4.0	4.0
Advanced planning necessary	1.6	1.8	4.3	4.2
Need to touch self	2.1	1.6	4.8	4.4
Side effects, health risks				
Dangerous	4.1	3.9	2.4	2.3
Increases health risks	3.7	3.9	1.9	1.8
Painful or uncomfortable to use	3.3	1.7	2.9	2.5
Anxiety or fear				
Increases anxiety about health	3.9	3.9	2.0	2.0
Increases fear of getting pregnant	2.1	1.7	3.1	3.6
Increases fear of losing control	2.9	2.3	1.6	2.5
Pregnancy/children				
Use results in pregnancy	1.8	1.6	2.6	3.0
Use results in sterility	2.0	1.8	1.4	1.3
Normative influences				
Advised against by family or friends	3.2	3.1	2.1	2.4
Advised against by MD	3.2	3.0	2.0	2.1
Leads to personal or sole responsibility for contraception	4.5	4.5	4.1	2.4

IUD = intrauterine device

*Responses were indicated on the following scale: 1 = very unlikely, 2 = unlikely, 3 = neutral, 4 = likely and 5 = very likely.

TABLE 3.—*Values of Respondents Toward Identified Concerns*

Issue of Concern	Mean Score*	Standard Deviation
Compromise moral/religious beliefs	− .59	.96
Interference with sexual activity	− .55	.55
Increased partner involvement	.39	.42
Inconvenient method	− .06	.39
Increased risk of adverse side effects	−1.33	.63
Increased fear or anxiety	−1.21	.65
Increased risk of pregnancy	−1.04	.86
Negative advice of friends, family, MD	− .34	.61
Personal responsibility for birth control	.01	1.12

*Responses were scored according to the following scale: −2 = very bad, −1 = bad, 0 = neutral, +1 = good and +2 = very good.

became more important concerns for older, married women of higher parity. Conversely, partner-related issues and the impact of pregnancy were of less importance to married, parous women.

Discussion

The findings of this study highlight the complexity surrounding contraceptive decision making. No single method was preferred by all women in this sample. Rather, the choice of a specific method varied with the age, marital status and parity of the respondents. Contraceptive decision making appears to be a dynamic, evolving process dependent on those variables related to a woman's life-style and situation.

Complexity is again revealed in an analysis of the estimates of likelihood and value judgments solicited in the questionnaire. Likelihood estimates varied according to the particular issue of concern and the contraceptive method under consideration. As the issues of concern were in large part negatively valued, the choice of a "best" contraceptive method seems to involve selecting the one least likely to incur undesirable consequences. When most of these consequences are perceived in a negative light, difficult trade-offs must inevitably be made.

TABLE 4.—*Values by Age of Respondents*

Issue of Concern	Age of Respondents (Years)			
	14-20 (N = 29)		21-45 (N = 77)	
	Mean Score*	Standard Deviation	Mean Score*	Standard Deviation
Compromise moral/religious beliefs	− .31	1.00	− .70	.92
Interference with sexual activity	− .38	.76	− .62	.43
Increased partner involvement	.40	.41	.38	.42
Inconvenient method	− .03	.56	− .08	.30
Increased risk of adverse side effects	−1.08†	.76	−1.42†	.55
Increased fear or anxiety	− .87†	.85	−1.34†	.50
Increased risk of pregnancy	−1.05	1.06	−1.03	.77
Negative advice of friends, family, MD	− .37	.84	− .33	.51
Personal responsibility for birth control	.21	1.11	− .07	1.12

*Responses were scored according to the following scale: −2 = very bad, −1 = bad, 0 = neutral, +1 = good, +2 = very good.
†$P < .05$

TABLE 5.—*Values by Marital Status*

Issue of Concern	*Single (N = 64)*		*Married (N = 32)*		*Separated/ Divorced (N = 10)*	
	*Mean Score**	*Standard Deviation*	*Mean Score**	*Standard Deviation*	*Mean Score**	*Standard Deviation*
Compromise moral/religious beliefs	− .48	.93	− .72	1.02	− .90	.88
Interference with sexual activity	− .52	.60	− .60	.49	− .62	.39
Increased partner involvement	.44	.40	.27	.44	.43	.39
Inconvenient method	− .05	.43	− .06	.34	− .17	.21
Increased risk of adverse side effects	−1.26	.67	−1.42	.56	−1.47	.53
Increased fear or anxiety	−1.14	.72	−1.32	.50	−1.30	.53
Increased risk of pregnancy	−1.22†	.90	− .66†	.70	−1.10†	.70
Negative advice of friends, family, MD	− .36	.70	− .27	.48	− .43	.39
Personal responsibility for birth control	− .05	1.05	− .03	1.23	− .10	1.29

*Responses were scored according to the following scale: −2 = very bad, −1 = bad, 0 = neutral, +1 = good and +2 = very good.
†$P < .05$

TABLE 6.—*Values by Parity*

Issue of Concern	*Parity*									
	0 (N = 77)		*1 (N = 12)*		*2 (N = 11)*		*3 (N = 4)*		*4 (N = 2)*	
	*Mean Score**	*SD*	*Mean Score**	*SD*	*Mean Score**	*SD*	*Mean Score**	*SD*	*Mean Score**	*SD*
Compromise moral/religious beliefs	− .50	.92	− .67	.98	−1.00	1.18	− .75	.96	−1.00	1.41
Interference with sexual activity	− .56	.59	− .40	.36	− .54	.47	− .81	.55	−1.00	0.00
Increased partner involvement	.43	.41	.31	.52	.30	.35	.17	.33	.17	.71
Inconvenient method	− .05	.42	− .04	.30	− .14	.28	− .31	.37	0.00	0.00
Increased risk of adverse side effects	−1.32	.67	−1.22	.50	−1.42	.60	−1.25	.32	−2.00	0.00
Increased fear or anxiety	−1.19	.69	−1.11	.41	−1.36	.66	−1.17	.43	−1.83	.24
Increased risk of pregnancy	−1.17†	.88	− .54†	.58	− .95†	.85	− .50†	.58	− .50†	.71
Negative advice of friends, family, MD	− .32	.67	− .33	.38	− .58	.45	− .08	.42	− .33	.47
Personal responsibility for birth control	− .01	1.10	.25	1.21	.09	1.30	− .50	.58	−1.00	1.41

*Responses were scored according to the following scale: −2 = very bad, −1 = bad, 0 = neutral, +1 = good and +2 = very good.
†$P < .05$

As most women were using a birth control method of their choice, it is still speculative as to whether these findings would hold for a population of unexperienced women seeking their first contraceptive method. Future studies should focus on this population for whom decision making might well be more problematic. Many of the younger respondents in this study requested more information regarding the methods mentioned. To be sure, making an intelligent decision presupposes that the necessary information surrounding that decision has already been obtained. The apparent informational gap hinted at in this study warrants further investigation and correction by concerned health care professionals.

The decision to use contraception is important, complex and value-laden. As such, an aid for selecting a contraceptive method may be useful in making explicit the underlying perceptions and values of the decision maker. Such clarification of values might serve to crystallize the information obtained or point out the need for further information before a decision could be made. To the clinician, such information might indicate a more appropriate and acceptable contraceptive choice. To the woman herself, such information could help to promote meaningful dialogue with her sexual partner of a wide variety of issues surrounding contraception.

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Low Prevalence of Hepatitis B Infections Among Residents of an Institution for the Mentally Retarded in New Mexico

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Residential institutions for the mentally retarded are considered high-risk settings for hepatitis B (HB) infection. Accordingly, HB vaccine is recommended for susceptible clients and selected staff of such facilities. However, a serologic screening program among 364 residents of Los Lunas Hospital and Training School (LLHTS) in New Mexico found only 11 residents to be anti-HBc positive (3%) and only one of these residents was also HBsAg-positive (0.3%). The unexpectedly low prevalence of HB infections at LLHTS probably reflects infrequent HB introductions into the institution. Using these serologic data, a vaccination program was instituted to prevent HB infection among LLHTS residents, thereby eliminating the need for mass screening and HB vaccination of LLHTS employees. Serologic screening among residents of other smaller institutions for the mentally retarded is recommended before design of HB prevention programs for clients and staff.

(Mann JM, Babb CJ, Hull HF, et al: Low prevalence of hepatitis B infections among residents of an institution for the mentally retarded in New Mexico. West J Med 1984 Sep; 141: 339-341)

Residential institutions for the mentally retarded have been considered a high-risk setting for hepatitis B (HB) infection.[1-7] In mid-1982, when hepatitis B vaccine became commercially available in this country, the US Public Health Service recommended that hepatitis B vaccine be administered to "susceptible clients and selected staff of institutions for the mentally retarded."[8] According to the Centers for Disease Control, residents of such institutions would be expected to have both a high prevalence of HBsAg-positivity (10% to 20%) and frequent serologic evidence of previous HB infection (35% to 80%).[8] Preliminary discussions with medical staff from Los Lunas Hospital and Training School (LLHTS), the largest state institution for the mentally retarded in New Mexico, suggested that HB infections might have been uncommon in this particular facility. Therefore, a serologic screening program was conducted to determine the prevalence of HB infection among residents and to help guide policies regarding use of HB vaccine at LLHTS.

Patients and Methods

Los Lunas Hospital and Training School

LLHTS is a state institution providing residential care for the severely and profoundly mentally retarded. The facility is located 20 miles south of Albuquerque. It opened in 1929 and resident capacity gradually increased from 76 in the late 1940s to a peak of 516 in the late 1960s. Deinstitutionalization efforts in the mid-1970s led to discharge of residents capable of living outside the institution. Consequently, current residents are severely or profoundly retarded and many are also

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ABBREVIATIONS USED IN TEXT

CDC=Centers for Disease Control
HB=hepatitis B
HBsAg=hepatitis B surface antigen
LLHTS=Los Lunas Hospital and Training School

multiply handicapped. Therefore, the current resident population is quite stable; from 1981 to 1983, an annual average of only 17 residents were admitted and 15 were discharged from LLHTS. At present approximately 360 residents live in 21 cottages, which range in capacity from 12 to 32 beds. Residents are grouped by level of functioning and age; some cottages are sex-segregated.

In addition to full-time residents, a respite program accepts short-term (not to exceed 60 days) institutional placement of clients normally living in the state. These temporary residents are housed with their functional and age-specific counterparts among the permanent residents. From July 1980 to June 1983 an average of 100 such short-term admissions occurred annually.

Of the 653 current LLHTS employees, 526 have direct contact with residents, as nurses, direct care staff, teachers, psychologists and other health and social service professionals. From 1981 through September 1983 annual staff turnover has averaged 30 percent. In addition to full-time staff, 80 older community residents participate in the Foster Grandparents Program and some ten part-time volunteers also work at the facility.

Serologic Screening Program

From September through November 1982 serum specimens (3 ml) were obtained from all current residents. Serum was frozen and shipped to the Scientific Laboratory Division (state laboratory) in Albuquerque. Anti-HBc testing was carried out on all specimens, using radioimmunoassay (CORAB; Abbott Laboratories, North Chicago, Illinois). Anti-HBc positive specimens were also tested for hepatitis B surface antigen (HBsAg) and anti-HBs by radioimmunoassay (AUSRIA II; AUSAB; Abbott Laboratories).

All anti-HBc-positive sera were sent to the Hepatitis and Viral Enteritis Laboratory of the Centers for Disease Control (CDC), where anti-HBc, anti-HBs and HBsAg testing was done for each specimen.

Information on each resident was abstracted from the patient's permanent record, including age, sex, ethnicity, date of admission to LLHTS, history of previous admissions to an institution, total years in institutions and major medical diagnosis.

Results

Characteristics of the Population

All current residents (364) were tested; there were 203 male and 161 female residents. Their ages ranged from 2 years to 69 years, with a median age of 25 years. Of the residents, 43% (155) were Hispanic, 41% (150) were white, non-Hispanic ("Anglo"), 13% (47) were Native American and the remaining 3% (12) were black, "mixed" or "other." (In 1980, 52.6% of New Mexico's population was Anglo, 36.3% was Hispanic, 8.1% was Native American and 2.9% was black or "other."[9]) Nearly three fourths (73%; 266) of the residents had never been admitted to another institution. Finally, the residents had been in an institution for periods ranging from one month to 48 years, with a median duration of 15 years. Only 18 residents (4.9%) had Down's syndrome.

Anti-HBc Serologic Results

Of the 364 residents 11 (3%) were anti-HBc-positive. Of these 11 there were 9 who were also anti-HBs-positive but HBsAg-negative, one who was both anti-HBs- and HBsAg-positive and one who was negative for both anti-HBs and HBsAg. Therefore, only one patient (0.3%) was HBsAg positive. Testing of HB markers at CDC agreed with Scientific Laboratory Division results in each case.

The HB-positive group included five men and six women ranging in age from 17 to 42 years, with a median age of 28.5 years. Four were Native American, four were Anglo and three were Hispanic. These patients had been in institutions from 7 to 28 years, with a median of 14.5 years; 5 of the 11 had been in institutions elsewhere before admission to LLHTS. None of the HB-marker-positive residents had Down's syndrome.

While 9% of Native American residents were anti-HBc-positive, compared with only 2% of Hispanic and 3% of Anglo residents, this difference was not significant. In addition, no significant differences between marker-positive and marker-negative residents were noted for sex, age, years in an institution, previous admission to an institution or major medical diagnosis (for example, Down's syndrome versus "other").

Discussion

The 3% anti-HBc and 0.3% HBsAg prevalence among residents of LLHTS contrasts sharply with published experience from other institutions for the mentally retarded in this country.[1-8] This difference could result from a limited ability of the serologic screening test (anti-HBc) to detect previous HB infections, since in most published studies anti-HBs plus HBsAg, rather than anti-HBc, were used as markers of past HB infection. However, anti-HBc was selected for LLHTS screening as the single serologic marker which would best identify current and recent HB infection, including chronic carriers.[8,10-12] In addition, anti-HBc appears to persist, in parallel with anti-HBs, for at least several years.[8,10-12] No single marker can provide a complete HB profile; yet while reliance on anti-HBc may underestimate the prevalence of much earlier HB infections, it nevertheless provides a reasonable index of HB activity at the LLHTS.

In other institutional studies, duration of institutional stays was most strongly and consistently associated

with increased HB marker prevalence.[3,4,6] Residents of LLHTS had been in institutions for a median of 15 years, so this factor cannot explain the low prevalence of HB infection at LLHTS.

The most plausible explanation for the low anti-HBc prevalence at LLHTS is a low rate of HB introduction into the facility. Recent data from nearly 10,000 first-time volunteer blood donors in New Mexico showed that only 0.03% were HBsAg-positive (personal communication, Toby Simon, MD, Medical Director, United Blood Services, Albuquerque, December 13, 1983), suggesting that HB infections in New Mexico may be relatively less common compared with other, particularly urban, areas of the country. The low anti-HBc prevalence at LLHTS could also be representative of smaller institutions while most published studies have involved large facilities[1-7] (approximately 800[2] to 3,600[3] residents). For example, a small (350-resident) institution in South Florida reported a 15% anti-HBc prevalence, which was recognized by the authors as unusually low for an institution for the mentally retarded.[13]

While a higher proportion of Native American residents of LLHTS were anti-HBc-positive compared with Hispanic or Anglo residents, the small numbers provide little basis for analysis. Specific data on HB among New Mexican Native Americans are not available. While a very small Arizona-based study of Navajo and Hopi found a low HB-marker prevalence,[14] systematic study would be required to elucidate HB patterns among the multiple distinct tribal groups in New Mexico.

Implications and HB Vaccination Policy at LLHTS

The LLHTS data suggest that generalizations about HB experience in residential institutions for the mentally retarded may not be applicable to all facilities. Therefore, design of an HB control program for a specific institution should be based on knowledge of the facility's particular problems and experience.

At LLHTS, the medical staff elected to administer HB vaccine to all HB-susceptible residents for several reasons. First, HB might enter the institution in the future, either from new long-term or short-term admissions from the community or from out-of-state institutional transfers. Entry of an HBsAg-positive client into a highly susceptible resident population would create substantial logistic problems, including the need for previous HB vaccination of the entrant's susceptible cottagemates and assurance that exposures of other residents to the potentially infectious new resident would be minimized. Second, prevention of HB among residents would reduce or eliminate the rationale for HB susceptibility testing and vaccination of more than 500 employees having direct contact with residents, along with nearly 100 foster grandparents and volunteers.[5,8,9] In addition to the cost of vaccinating current staff, the institution's high employee turnover rate would ensure a considerable expense if ongoing testing and vaccination programs were required.

At LLHTS, once vaccination of the stable resident population is completed, serologic screening of new admissions will identify susceptible persons for vaccination and HBsAg-positive entrants for special management. Staff likely to have regular contact with an HBsAg-positive person newly admitted will be educated regarding HB transmission and its prevention. Depending upon an individual assessment of the HBsAg-positive new resident (including HBeAg and anti-HBe testing and consideration of behavioral and medical characteristics) a limited program of serologic screening or HB vaccination of staff could be implemented, if required. (This approach has already been applied to the single HBsAg-positive resident identified in the screening program. Since the resident was not aggressive, anti-HBe-positive and HBeAg-negative, he was considered unlikely to transmit HB and only educational precautions for certain staff were judged necessary.) Finally, if a substantial number of HBsAg-positive persons were to be newly admitted to LLHTS in the future, this individually tailored and limited approach to HB risk management for staff would be reconsidered.

In summary, serologic screening for HB among residents of smaller institutions for the mentally retarded is recommended since it may provide useful information for design of a rational HB prevention program for clients and staff.

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Chest Pain in Adolescents—Functional Consequences

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In prospectively evaluating 100 cases of adolescents with chest pain (along with two control groups), 91 were found to have recurrent chest pain; fewer than 5 had a serious organic cause. Significantly higher school absenteeism occurred in patients with either chest or abdominal pain than in patients without pain. Adolescents with chest and abdominal pain were more likely to be high users of medical services than those with no pain. Most adolescents believed that persons their age could have heart attacks; 44 of those with chest pain thought their symptom was due to a heart attack. The occurrence of chest pain was not influenced by an adolescent's age, sex, race, smoking status or family structure, nor was it consistently associated with depression. Chest pain is thus a common problem of adolescence that produces considerable functional impairment not attributable to serious underlying disease.

(Goodman BW Jr, Pantell RH: Chest pain in adolescents—Functional consequences. West J Med 1984 Sep; 141:342-346)

Chest pain is a symptom that not only causes considerable concern for adults but is a problem for children and youths. Each year physicians see 650,000 episodes of chest pain in patients 10 to 21 years old.[1] The true incidence is unknown as most cases are never brought to medical attention. Only in recent years have investigators focused attention on the cause of chest pain in younger patients. Studies have shown that fewer than 10% of patients have serious underlying disease.[2-4] The morbidity and functional impact of chest pain, however, and adolescents' beliefs about this symptom have not been explored. Studies in adults have shown that nearly three quarters of patients with chest pain who had normal findings on coronary arteriograms limited their daily activities and more than half were incapable of working.[5] Similarly, the morbidity of "cardiac nondisease" in schoolchildren was shown by Bergman and Stamm, who found 40% of children with no heart disease (often only an "innocent" murmur) to be restricted in some way.[6] Because of the perceptual linkage between chest pain and the heart, these findings are not surprising.

The purpose of our study was to determine the extent and impact of chest pain in an adolescent population. Functional consequences examined included school attendance, the use of clinical services, health perception, depression and the occurrence of other somatic complaints. We prospectively evaluated 100 cases of adolescents seeking care for chest pain in an ambulatory setting. For purposes of the study we established two control groups—100 patients presenting with abdominal pain and 100 patients seeking care for problems not causing pain.

These groups were prospectively evaluated to establish comparative data that would enable us to interpret the role of social and medical factors predisposing patients to chest pain. The comparison groups also permit evaluation of the functional impairment attributable to chest pain.

Methods

This study was conducted at the Adolescent Clinic at the Medical University of South Carolina, Charleston. The clinic principally provides comprehensive primary care, with referrals from other agencies accounting for less than 10% of patient visits. All pa-

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TABLE 1.—*Demographic Profile of Clinic and Study Adolescents*

	Clinic Population N = 1,085	*Chest Pain N = 100*	*No-Pain N = 100*	*Abdominal Pain N = 100*
Age (mean)	16.2	16.4	16.0	16.2
Race/black (%) ..	89	91	92	92
Sex/female (%) ..	67	63	64	79

TABLE 2.—*Adolescents' Perceptions of General Health*

Responses to Questions	*Control (N = 100) Percent*	*Chest Pain (N = 100) Percent*	*Abdominal Pain (N = 100) Percent*
My health			
is generally good	66	40	44
[I have] some minor problems	34	55	56
is poor	0	5	0
My health interferes with school			
never	58	33	26
sometimes	37	50	58
often/a great deal	5	17	16

tients requesting general appointments are seen in this clinic, which meets twice a week. Consequently, this series of patients consists mostly of adolescents who do not have acute problems.

The age, sex and race of the clinic population and study groups are given in Table 1. Clinic patients are predominantly black and a mixture of urban and rural dwellers. Of these, 80% qualify for medical assistance (an annual income of less than $4,925 for a family of four).

Study Participants

Patients with chest pain. To be included in this series, all patients must have had pain in their chest as either the first or second reason for coming to the clinic. Adolescents completed a written health history form at the time of the visit immediately before medical evaluation. During the period from January 1979 to April 1981, 100 different patients were seen for chest pain. The largest single group had chest pain for which no etiologic classification was identified (39%); musculoskeletal pain accounted for 31%, hyperventilation occurred in 20%, breast problems in 5%, gastrointestinal problems in 2% and mitral valve prolapse in 1%. Only two patients had acute (respiratory) problems. In all, 91% had recurrent chest pain. This group and the basis for this etiologic classification are further described elsewhere.[4]

Patients without pain. A total of 100 patients without any complaint of pain were randomly selected from March 1980 to April 1981 as a second control group. Of these patients, 86 requested a physical examination, 6 came for contraception, 2 had breast concerns and 1 each was seen for acne, asthma, allergic rhinitis, irregular menses, immunization and urticaria. These patients completed the health history questionnaire before examination.

Patients with abdominal pain. A sequential control group of 100 consecutive patients with abdominal pain was studied. These cases were collected in 18 months. To be included in this series patients had to have abdominal pain as the first or second symptom motivating them to seek medical care. They also completed the written history form before examination.

Procedure

At the time of initial visits all adolescents who came to the clinic and all patients in the three study groups were asked to complete a 104-item pretested questionnaire. We sought to elicit demographic data (6 items), perception of general health (4 items), information about self-esteem and symptoms of depression (8 items), school performance (10 items), family structure and function (6 items), peer relationships (6 items), requests for health information (10 items), review of systems and past medical history (32 items), sexual development (14 items), substance use and personal habits (8 items). The reliability of this type of instrument has been reported elsewhere.[7] Test-retest reliability for selected items in our instrument was comparable; concordance for all items was greater than 90%. Questions about depressive symptoms were based on criteria for diagnosing depression outlined in *Diagnostic and Statistical Manual of Mental Disorders* (DSM III). All patients were clinically evaluated by either of the two authors. The use of medical services was determined by reviewing adolescent clinic records; visits for obstetric or emergency care or care in other facilities were excluded from the analysis.

Results

Incidence

During the period from January 1979 to April 1981, the cases of 100 different patients were evaluated specifically for chest pain. During the same period an aggregate of 1,085 patients was seen in the clinic, making the period incidence 9.2%. Of all adolescents responding to the written questionnaire, 51.9% recalled having chest pain in the past; 26.5% claimed to have had more than three episodes in the previous year.

Characteristics of Groups

Demographics. Table 1 shows the age, sex and race of patients in the three study groups as well as the clinic population. Chest pain patients did not differ from the other groups in either age or race. There were more girls in the abdominal pain group than would be expected by chance (χ^2, 2 *degrees of freedom* [*df*], = 7.46, $P < .02$). Adolescents with chest pain were no more likely to come from single-parent families (44%) than adolescents in the two control groups.

Drug and medication usage. Smoking occurred no more frequently in patients with chest pain (18%) than in the control groups (12%). Also, no detectable differences were seen in the reported use of oral contraceptives, medications, alcohol or street drugs.

Functional Consequences

General health. Compared with the no-pain control group, adolescents with either chest pain or abdominal

pain were more likely to view their overall health as problematic (χ^2, 4 df, = 28.4, $P < .001$) and also as causing dysfunction by interfering with school (χ^2, 4 df, = 26.8, $P < .001$). This is shown in Table 2.

School. The ways in which health problems interfered with an adolescent's promotion and attendance in school are displayed in Tables 2 and 3. There were no differences in the three groups in the percentage of persons who ever repeated a grade. However, overall school attendance (χ^2, 2 df, = 11.81, $P < .01$) was adversely affected in both pain groups. Patients with chest pain were significantly more likely to report they stayed home from school because of this symptom (χ^2, 2 df, = 68.5, $P < .001$). Because of the importance of school in an adolescent's life, school absenteeism is a critical marker for the functional impairment imposed by a symptom. We conducted an additional analysis to compare those adolescents with chest pain who claimed to miss school three or more times a month (N = 32) with those absent two times or less (N = 68). Girls were more likely to be in the high- than the low-absenteeism group than could be accounted for by chance alone (84% versus 53%; $\chi^2 = 8.28$, $P < .01$). Those in the high-absenteeism group were also more likely to feel that their health often interfered with their ability to function in school compared with the low-absenteeism group (34% versus 9%) ($\chi^2 = 10.1$, $P < .01$).

Symptoms of depression and reporting of family problems. Significantly more adolescents with chest pain (65%) and abdominal pain (55%) were worried about themselves than patients without pain (34%) (χ^2, 2 df, = 20.9, $P < .001$). More patients with chest pain (48%) and abdominal pain (42%) felt self-reproach that they were unable to do things as well as peers than did patients without pain (26%) (χ^2, 4 df, = 17.0, $P < .01$). However, there were no differences among the three groups in reporting insomnia, anorexia, fatigue, feeling loss of pleasure or noting psychomotor retardation. While patients in the high-absenteeism and chest pain group consistently admitted to more symptoms of depression, this increase was not statistically significant. Depression, based on the clinical assessment of a dysphoric mood, in addition to affirmative questionnaire responses, was found in 7% of patients with chest pain. Statistical power at this low rate is insufficient to make valid comparisons with the control groups.

No group differences were noted in response to a question whether the adolescents were troubled with family problems or whether they wished help for family problems.

Review of systems. In reviewing the systems, we were particularly interested in the reporting of the occurrence of another pain symptom, headache. While the three groups reported similarly for the past occurrence of headache, frequent headaches (once a month or more) occurred in a significantly higher percentage of those with abdominal pain (58%) than in the chest pain (44%) and no-pain groups (38%) (χ^2, 2 df, = 8.4, $P < .05$). Patients with abdominal pain also missed school more often for headaches (32%) than patients in the other groups (19%) (χ^2, 2 df, = 13.26, $P < .01$). Of the 32 patients with chest pain in the high-absenteeism group, 20 admitted to having missed school due to headache; none of the 68 patients with chest pain and low absenteeism had absence due to headache ($\chi^2 = 50.9$, $P < .001$).

Use of clinic services. The use of clinic services was compared for the three groups. The National Ambulatory Medical Care Survey documented that adolescents make 2.1 office visits a year.[3] For purposes of this analysis we defined high usage as more than four visits a year. Adolescents with chest pain and abdominal pain were more likely to be high users (57% and 60%, respectively) than those with no pain (27%) (χ^2, 2 df, = 25.1, $P < .001$). While only 6% of patients with no pain were high users for two consecutive years, 11% of adolescents with chest pain and 15% with abdominal pain were in this category. Adolescents in this high-use group visited the clinic on an average of 6.7 times a year excluding obstetric care; the range was from 8 to 37 visits in a two-year period.

Illness Attributions

All study participants were asked the question, Do you believe people your age can have a heart attack? Adolescents with chest pain (78%) and abdominal pain (74%) were more likely to respond affirmatively than those without pain (61%) (χ^2, 2 df, = 7.6, $P < .05$). Of those patients who came to the clinic for evaluation of their chest pain, 44% were afraid they had had a heart attack, 12% were worried about heart disease and 12% feared cancer.

The findings of group similarities and differences are summarized in Table 4.

Discussion

In our clinic, chest pain was the fourth most frequent symptom encountered, with more than 9% of the pa-

TABLE 3.—*Self-Reported School Functioning of Chest Pain and Control Groups*

	No Pain (N = 100) Percent	*Abdominal Pain (N = 100) Percent*	*Chest Pain (N = 100) Percent*	*Chest Pain*	
				High Absenteeism (N = 32) Percent	*Low Absenteeism (N = 68) Percent*
Repeated a grade	42	40	47	41	50
Absent ≥3 days a month	16	37	32	100	0
Headache absence last year	18	32	20	63	0
Chest pain absence past year	2	6	41	...	...

tients specifically seeking care for this problem. More than half of the 1,085 adolescents surveyed recalled having chest pain; more than a quarter had three bouts in the past year. In an area probability sample in which 562 urban black adolescents were surveyed, chest pain was the seventh most common problem occurring in 12.8% of patients.[8] Only 32% of these youths saw a physician. In Driscoll's nine-week survey of all pediatric patients seen in Milwaukee Children's Hospital, 43 children aged 5 to 19 years (mean, 12.3 years) presented with chest pain for a visit rate of 0.3%.[2] The denominator contains numerous infant visits and therefore underestimates the true prevalence of chest pain, a symptom requiring the descriptive skills of older children. The National Ambulatory Medical Care Survey, with a denominator including newborn infants to patients 21 years old records 0.4% of visits for chest pain.[1] In another series from an adolescent clinic, at least 5% of visits were for chest or upper abdominal pain.[3] Whereas abdominal pain occurred more than twice as often as chest pain in our clinic, patients were seen for evaluation of chest pain slightly more frequently than for headache and considerably more frequently than for back pain.

We conceived this study because we were struck with what seemed to be an increasing number of adolescents complaining of chest pain. Lack of systematic data collection nationally prevents us from knowing whether or not this is a nationwide trend. There are two possible explanations for an increasing number of adolescents seeking care for chest pain. An increasing number of patients may be having this symptom or are now interpreting this symptom to be severe enough to require medical attention. The latter reason may be likely considering our current national concern with heart disease. The vast majority of adolescents in all our study groups believed they were susceptible to heart attack and two thirds of those presenting with chest pain attributed their symptom to heart disease.

Several implications arise from our finding that chest pain is so common in this group of adolescents. Because chest pain experienced when taking birth control pills may be due to a pulmonary embolus or esophageal effects of the progesterone component, adolescents are often told to call their physicians immediately for severe chest pain.[9] Because "severe" is a subjective perception, and as most adolescents have already had chest pain, it is important for physicians to elicit an adolescent's precontraceptive chest pain history and to recommend contact if the quality of their preexisting chest pain changes.

Chest pain has also been interpreted as a symptom that signals those patients with mitral valve prolapse who need treatment.[10] Adolescent chest pain is so common we would expect most patients with a prolapsed valve to have chest pain. The causal link is unclear, however. Indeed, a controlled study in adults has shown that chest pain occurred no more frequently in patients with mitral valve prolapse than in matched normals.[11]

The burden of chest pain to the group of adolescents we studied was considerable. They were more worried about themselves than were healthy controls and had more limitation of activity and an increase in school absenteeism. These functional limitations associated with chest pain are noteworthy, especially in the absence of significant organic disease in this group of patients and in those in other published series.[2-4] Their concerns about themselves are not surprising given their beliefs about the cause of their symptom.

One of our concerns was to determine whether chest pain in adolescents represented a proxy for persons who seemed more prone to pain or who expressed complaints of pain in many systems. Adolescents with abdominal pain did have more frequent headaches and headache absenteeism than did the nonpain controls or patients with chest pains. Adolescents with chest pain were no more likely than the healthy control groups to have had headaches, frequent headaches or absenteeism from school due to headaches. When a subset of adolescents with chest pain and frequent school absenteeism was identified, however, they had significantly more headache-related absence. This group may indeed have had more pain, a lower threshold for tolerating pain or fewer skills in coping with pain.

Another purpose of the control group was to determine whether or not chest pain might be a marker for

TABLE 4.—*Characteristic Features of Groups*

Features Similar in All Groups	*Pain Groups*	*Chest Pain*	*Abdominal Pain*
Age	More school absenteeism	More absenteeism for chest pain	More likely to be female
Race	High clinic utilization		More "frequent" headaches
Family structure	Health perceived as problematic		More headache absenteeism
Smoking	Health interferes with school		
Medication use	Activities limited		
School failure	More worried		
Headaches (ever)	More self-reproach		
Anorexia			
Insomnia			
Feels useless			
Loss of pleasure			

underlying depression. In a recent report chest pain was suggested as an accompanying symptom of depression in some children.[12] This conclusion was based on finding depression in all four children with chest pain referred to a pediatric cardiology clinic compared with 13% for the series of 100 children referred to the same clinic, all for cardiac conditions. Using similar criteria, 1.9% of children are considered to have depression.[13] In our series, clinical depression, based on affirmative responses to the questionnaire and a clinical assessment of a dysphoric mood, was diagnosed in only 7% of patients. Thus, whereas a small subset of patients were clinically depressed, chest pain was not consistently associated with symptoms of depression. However, patients with chest pain were no more likely than healthy adolescents to report most of the symptoms characteristic of depression.

Adolescents with chest pain resembled those with abdominal pain in their frequent use of the clinic. Underlying reasons for high use have been reviewed by Barsky and include psychiatric disorders, inordinate discomfort, life stress and illness attribution.[14] In Driscoll's series in which 43 patients had psychiatric evaluation, there was no evidence of underlying psychiatric disturbance.[4] Adolescents with functional abdominal or chest pain have a greater amount of stress as reflected in a higher frequency of negative life events than well or acutely ill controls.[15] Finally, the illness attribution we have documented helps to understand the high use of the clinic in this group. A single visit may not be enough to reassure an adolescent who believes the recurrent pain is due to heart disease or cancer.

In summary, chest pain is a common problem that in our population created considerable burdens for adolescents, including high school absenteeism, perceptions of poor health and frequent clinic use. The occurrence of the problem was not influenced by an adolescent's age, sex, race, smoking status, family structure or perception of family problems. We did not find chest pain to be associated with a higher-than-expected frequency of another somatic complaint, headache. Chest pain was not consistently associated with depression, though some depressive symptoms were seen more often than in healthy controls, and some patients were clinically depressed.

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Medical Progress

Pain—Mechanisms and Management

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In the past two decades there has been remarkable progress in understanding the neural mechanisms of pain. However, chronic pain is poorly understood and, by definition, poorly managed. In addition to hyperactivity of the sympathetic nervous system and damage to normal inhibitory mechanisms, social and psychological factors play a major role in producing the disability of chronic pain. New approaches to manage chronic pain include nonopiate drugs, transcutaneous electrcal nerve stimulation and psychological and behavioral methods. A nervous system network has recently been described that suppresses pain. This analgesic action is mediated by endogenous opioid peptides (endorphins) and by biogenic amines. The analgesia network can be activated either by electrcal stimulation or by opiates such as morphine or methadone.

(Fields HL, Levine JD: Pain—Mechanisms and management [Medical Progress]. West J Med 1984 Sep; 141:347-357)

Pain is a warning signal that helps to protect the body from tissue damage. Potentially damaging stimuli activate and sensitize certain primary afferent nerve cells. The activity of these nerve cells projects to the spinal cord and from there to the brain, giving rise to the sensation of pain. Clinically, the sensation of pain elicits varying degrees of suffering and depression depending on its duration and a patient's psychosocial environment.

In the past two decades there has been rapid progress in our understanding of the physiology of pain. In this review we will first briefly outline current concepts of the mechanisms of pain transmission and modulation, then focus on those areas of pain management where concepts have changed, where new scientific findings have been applied to patient care or where existing knowledge has not been applied optimally.

Pain Transmission System

The first step leading to the sensation of pain is the activation of nociceptive primary afferents by intense thermal, mechanical or chemical stimuli. The mechanism of this activation (transduction) is poorly understood because the receptive region of the nociceptor is located in small, diffusely distributed, free nerve endings. Indirect studies of nociceptive transduction indicate that it involves chemical mediators that are released or synthesized in response to tissue damage (Figure 1). Physiologic concentrations of such inflammatory mediators either directly activate or sensitize nociceptors.[1] Because any intense stimulus could produce slight tissue damage, it is possible that such stimuli activate nociceptors through a common mechanism involving these mediators. A major breakthrough in our understanding of the transduction process was the finding that prostaglandins contribute to the activation of primary afferent nociceptors. Acetylsalicylic acid or other nonsteroidal anti-inflammatory agents (NSAIAs) prevent pain by inhibiting the metabolism of arachidonic acid to prostaglandins.[2] Other inflammatory mediators such as leukotrienes have also been shown to produce pain.[3] Because the cyclooxygenase pathway of arachidonic acid metabolism is not involved in leukotriene production, usual doses of NSAIAs do not prevent its production in injured tissue. Thus, the development of agents that block leukotriene synthesis could extend the clinical usefulness of NSAIAs.

The transduction process in the peripheral terminals

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ABBREVIATIONS USED IN TEXT

NSAIA = nonsteroidal anti-inflammatory agent
TENS = transcutaneous electrical nerve stimulation

of primary afferents leads to action potentials in their axons which propagate to the spinal cord. Sensory axons in a peripheral nerve fall into discrete groups based on diameter and conduction velocity. The most numerous group consists of the unmyelinated axons (C-fibers) that conduct very slowly (less than 3 ms^{-1}). They constitute 80% of all axons in cutaneous nerves. Most unmyelinated afferents can be activated by noxious stimuli. There are several groups of myelinated afferent axons, but only the smaller diameter, slower conducting ones are sensitive to noxious stimuli. The large-diameter myelinated sensory neurons respond maximally to innocuous stimuli.

In the spinal cord, the small-diameter sensory axons, which include all known nociceptors, enter the gray matter of the superficial dorsal horn to synapse on nerve cells contributing to pain-transmission pathways such as the spinothalamic tract (Figure 2). Besides pain-transmission neurons (projection cells), there are at least two other types of neurons located within the superficial dorsal horn (interneurons): one type relays information from primary afferents to the projection cells, the other *inhibits* the relay of information to the projection cells.[4,5] The inhibitory interneurons alter the pain message as soon as it enters the central nervous system (see Figure 2). Thus, although there are primary afferents specifically activated by noxious stimuli, the sensation of pain is a complex sum of activity in both nociceptive and nonnociceptive afferents.

One of the important controls over nociceptive transmission is exerted by the large-diameter primary afferents that respond to innocuous stimuli. These large myelinated afferents activate inhibitory interneurons that control pain transmission.[6,7] The functional importance of this inhibition is shown by the observation that when the large-diameter myelinated afferents in a nerve are blocked, the activity of the functioning unmyelinated afferents in the same nerve produces pain that is more severe than occurs when the myelinated afferents are conducting normally.[8,9] It is important to remember that when noxious stimuli are applied, *both* large- and small-diameter sensory fibers will be activated—that is, an intense stimulus will activate fibers that are also activated by mild stimuli. Thus the large-diameter myelinated primary afferents will normally *inhibit* the dorsal horn neurons that are excited by nociceptive primary afferents (Figure 2). This inhibitory effect explains the analgesic effect of transcutaneous electrical nerve stimulation (TENS) which selectively activates large fibers.

Our knowledge of the physiology of primary afferent nociceptors has been expanded by the recent discovery that they contain a variety of polypeptides. Substance P, somatostatin, vasoactive intestinal polypeptide and cholecystokinin are all present in different populations of small-diameter unmyelinated primary afferents, all of which terminate in the superficial dorsal horn.[10,11] Substance P is the best studied of these peptides. It excites pain-transmission neurons in the dorsal horn.[12] When the neurotoxin capsaicin is used to destroy substance P-containing primary afferent neurons, animals become unresponsive to a variety of noxious stimuli.[13] The role of the other neuropeptides in pain is less well understood.

In addition to its proposed role as a neurotransmitter at the spinal cord terminals of nociceptors, substance P is also transported toward the peripheral terminals of these neurons.[14] Release of substance P from the peripheral terminals of nociceptors can produce cutaneous wheal and flare, a neurally mediated response

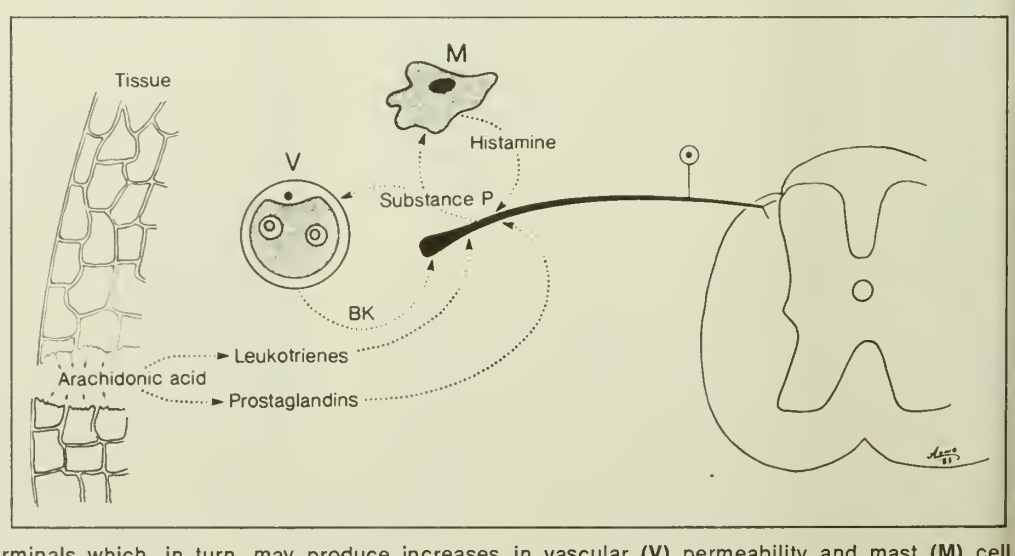

Figure 1.—A schematic representation of a primary afferent nociceptor—which transmits pain signals from injured tissue to dorsal horn of spinal cord—and its interaction with mediators of acute inflammation. Tissue injury stimulates the production of mediators or directly releases them from tissue stores. Mediator effects on primary afferent nociceptors include direct *activation* of the nociceptive afferent by bradykinin **(BK)** or histamine, and *sensitization* of the nociceptive afferent by prostaglandin products of arachidonic acid metabolism. The activated nociceptor releases neuropeptides such as substance P from its peripheral terminals which, in turn, may produce increases in vascular **(V)** permeability and mast **(M)** cell degranulation.

that occurs following noxious stimulation.[15] The inhibition of the peripheral actions of substance P by specific antagonists could provide a new therapeutic approach to the control of inflammation and pain. A number of antagonists for substance P have already been synthesized with this in mind.[16,17]

The processes initiated by noxious stimuli produce activity in pain-transmission neurons in the dorsal horn of the spinal cord that leads to a coherent message that is relayed to the brain. There are at least two major pathways in the spinal cord that are involved in this rostral projection of the pain message: the well-known spinothalamic tract and the larger but less appreciated spinoreticulothalamic tract. The latter tract runs with the spinothalamic tract in the spinal cord but separates from it in the brain stem to synapse on neurons in the reticular formation that in turn project to the thalamus. We know very little about differences in the function of these two pathways; however, there is some suggestion that activity transmitted via the spinoreticular pathway arises predominantly from deep and visceral structures.[18] Activity in the spinoreticular pathway may produce the more diffuse and emotionally disturbing pains that accompany many clinical conditions.[19]

These two pain pathways also have different sites of termination within the thalamus. The spinoreticulo-

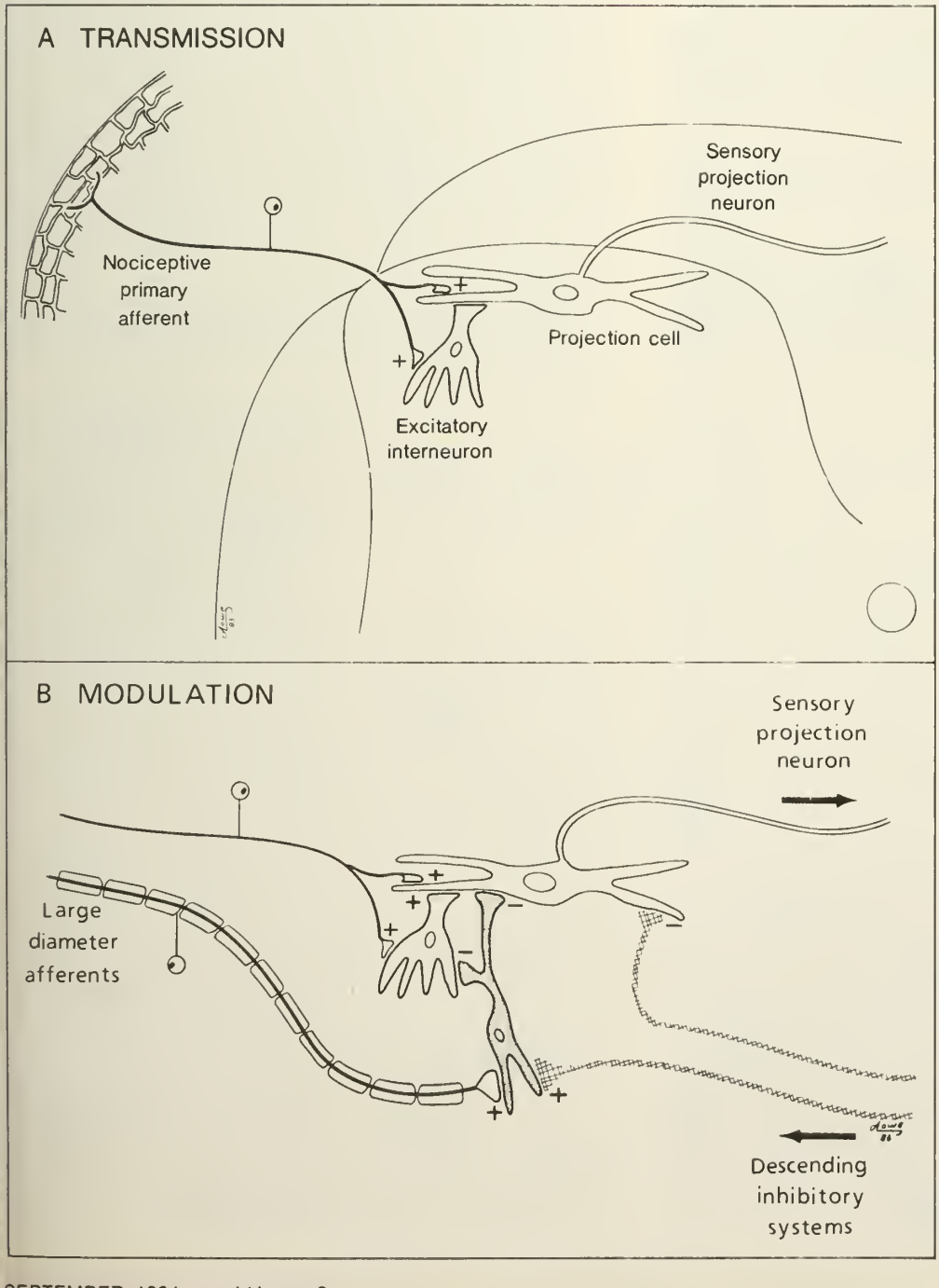

Figure 2.—A, A schematic representation of the central connections of the nociceptive primary afferent and projection cells in the pain-transmission pathway. In the dorsal horn of the spinal cord, nociceptive afferents synapse onto both projection cells that transmit pain signals rostrally to terminate in the thalamus, and onto local neurons that in turn synapse onto projection cells.

Figure 2.—B, A schematic of dorsal horn pain circuits including local (stippled) and descending (crosshatched) inhibitory systems. The local dorsal horn pain-inhibitory system can be activated both by descending inhibitory systems and by the large-diameter myelinated primary afferents that respond to nonnoxious stimuli. The plus (+) sign indicates an excitatory connection and the minus (−) sign an inhibitory synaptic connection between two neurons.

thalamic projection is more medial and the direct spinothalamic projection primarily lateral, ventral and caudal. The two thalamic regions project to different cortical sites, though in humans these sites are still unknown. It is established, however, that there is a cortical "representation" for pain because cortical and spinal and thalamic lesions can greatly impair the perception of pain.

Pain-Modulation System

The most important recent advances in our understanding of pain have come from the discovery of a specific central nervous system network for pain control and of endogenous opioid substances (referred to generically as endorphins) that are synthesized by nerve cells and have pharmacologic properties nearly identical to narcotic analgesic drugs. These discoveries have provided a basis for understanding the clinically well-known but scientifically puzzling variability of perceived pain.

The key observation leading to the discovery of the endorphin-mediated analgesia system was of the phenomenon of stimulation-produced analgesia. First described in rats, it occurs when certain parts of the brain are electrically stimulated. The inhibition of pain that occurs during stimulation is strikingly selective. Although animals are alert, active and respond normally to innocuous stimuli, noxious stimuli do not produce the expected vocalization, biting and escape. Its selectivity for pain received crucial confirmation from observations of patients with intractable pain who have had stimulating electrodes implanted at sites homologous to those from which stimulation-produced analgesia was elicited in animals.[20] Many patients with these electrodes report a gradual melting away of their pain. Although some report a feeling of warmth or sleepiness (or both), no other effects are consistently associated with pain relief. Thus, the system activated appears to be specifically designed for controlling pain.

Subsequent research has elucidated the anatomic, chemical and physiologic basis for this pain modulation. In Figure 3 is outlined what is known of its anatomy. The pain-modulating network consists of a series of neurons that run from the cortex to the dorsal horn of the spinal cord. Anatomic and physiologic studies have established that sites in the hypothalamus, midbrain periaqueductal gray and rostral medulla are also involved.[21,22] Although not tested in humans, electrical stimulation at the medullary level in animals produces analgesia and inhibits nociceptive spinothalamic tract cells. Thus the selectivity of the pain-modulating network apparently derives from its inhibition of spinal cord pain-transmission cells.

About the time that this pain-modulation network was being mapped, a parallel revolution was occurring in the world of pharmacology. Structure-activity rela-

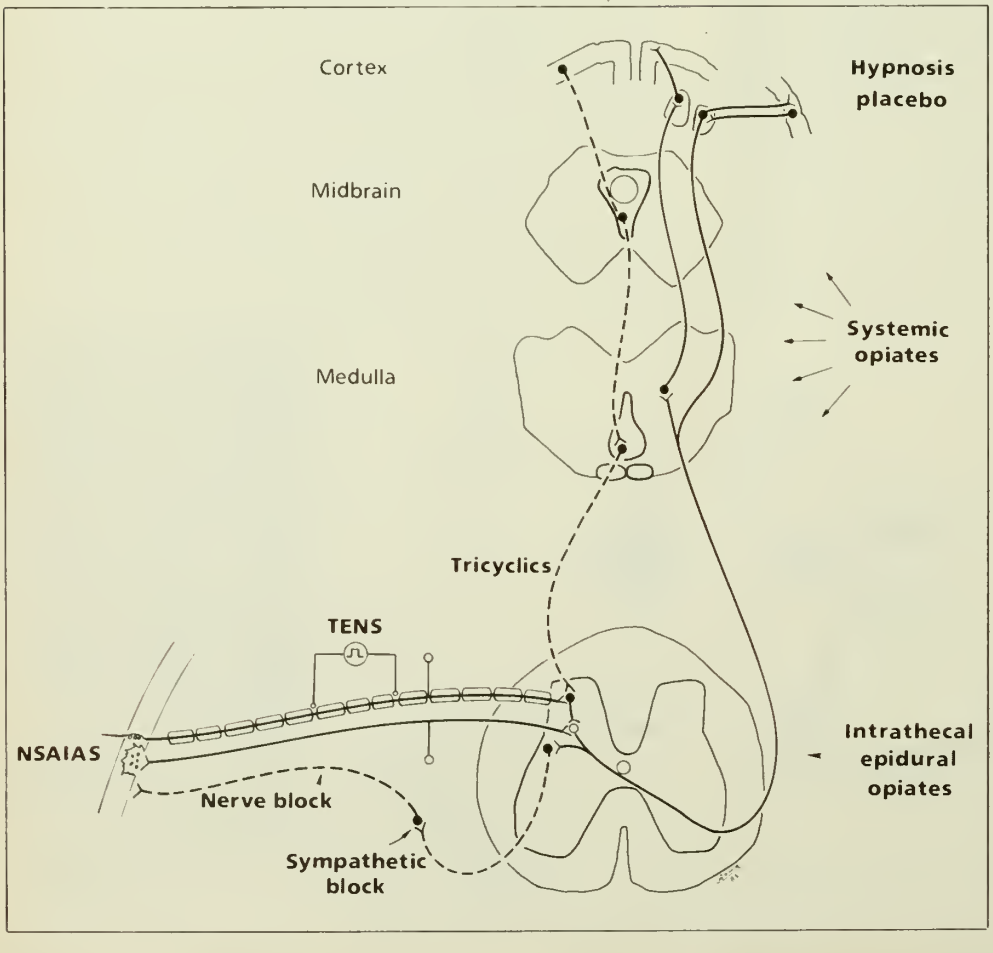

Figure 3.—A detailed schematic of the sites of action of commonly used pharmacologic and physiologic analgesic therapies. The aspirin-like nonsteroidal anti-inflammatory analgesics (NSAIAs) act at the level of the transduction process in the nociceptive primary afferent. Sympathetic blocks may have a similar locus of action. Peripheral nerve blocks work by blocking transmission. Transcutaneous electrical nerve stimulation (TENS) produces analgesia indirectly by activation of large-diameter afferents that normally respond to nonnoxious stimuli. These afferents, in turn, activate local analgesia circuits in the spinal cord and may also inhibit the sympathetic nervous system. Opiate analgesics act at multiple sites in the central nervous system to activate the descending inhibitory systems (shown by broken line). Application of opiates at the level of the spinal cord produces local analgesia. Tricyclic antidepressants appear to produce analgesia by an action on the same descending inhibitory system that mediates opiate-induced analgesia. This system may also be activated by suggestion and hypnosis via cortical circuits.

tions for clinically effective narcotic analgesics had been well worked out and bioassays were available to assess new opiate-like drugs.[23] The analgesic potency of these narcotic drugs was shown to correlate well with their binding affinity to certain membrane preparations from brain. This binding was shown to be stereospecific and to have a high affinity. In addition to the binding-potency relationship, the availability of a selective antagonist, naloxone, allowed these binding sites to be clearly identified as opiate receptors. This triggered the search for an endogenous ligand for the opiate receptor. In 1975 Hughes and co-workers[24] reported that two pentapeptides isolated from pig brain had a high affinity for the opiate receptor. These pentapeptides were active in bioassays and their action was blocked by the narcotic antagonist, naloxone. These two pentapeptides, leucine and methionine enkephalin, were the first endorphins discovered. It is beyond the scope of this review to enumerate all of the endorphins, their anatomic distribution, putative functions and metabolism. It is, however, important to point out that there are at least three distinct families of endorphins coded by separate genes and present in different cell populations of brain, pituitary, adrenal, gut and sympathetic nervous system.[25]

Many of the endorphin-containing cells of the brain are anatomically associated with the analgesia networks described above. For example, the enkephalins are present in nerve cells at midbrain, medullary and spinal loci implicated in pain modulation. Furthermore, there is a remarkably precise anatomic correlation between opiate receptor, endorphin distribution and the nuclei from which analgesia can be elicited by electrical stimulation or microinjection of opiates. This evidence provides convincing support for the idea that there is a discrete endorphin-mediated network designed specifically for modulating pain.

In addition to providing both an anatomic and a chemical explanation for the phenomenon of stimulation-produced analgesia, the discovery of the endorphin-mediated analgesia system has provided insights into how narcotic analgesics relieve pain. Thus, drugs like morphine sulfate, meperidine hydrochloride and Percodan (oxycodone hydrochloride and aspirin) presumably relieve pain by mimicking the action of endorphins at synapses in the pain-modulating networks.

Despite the importance of endorphins, it would be misleading to suggest that they are the only neurotransmitters involved in pain modulation. There is a good deal of evidence that both norepinephrine and serotonin also play a role, especially in the connection between the brain stem and the spinal cord.[26,27] These transmitters are of particular importance because they can be manipulated by a variety of pharmacologic agents, thus raising the possibility of new classes of centrally acting analgesic agents.

Perhaps the most important unanswered questions concerning the endogenous opioid-mediated analgesia system relate to its physiologic functions. Why does the brain need this pain-modulating system? When is it activated? How are its actions manifest? At the present time, our answers are teleologic or simply descriptive. Part of the problem is that we are dealing with a modulatory system whose activity is best studied in patients with clinically significant pain.

Early studies of nerve cells in the nuclei involved in pain modulation indicated that the majority were excited by noxious stimuli. This suggested that the network might function simply as a negative-feedback system to dampen responses to painful stimuli. Thus, if a given noxious stimulus activates both transmitting and modulating networks, the pain is less severe than it would be if only the transmission system were activated.

Because it is difficult to directly study the activation of the modulatory system in humans or in awake animals, this hypothesis required an indirect approach for its confirmation. Assuming that the action of endogenous opioids would be antagonized by administration of the narcotic antagonist, naloxone (Narcan), researchers used naloxone to block the analgesia network. The results of such studies have led to a tentative formulation of how the analgesia network is activated.

The responses to brief superficial painful stimuli are not altered by naloxone.[28,29] Noxious stimuli must be above the pain threshold and have prolonged duration to produce analgesic actions that are blocked by naloxone. Second, stimuli that are stressful, inescapable or associated with anxiety are particularly effective for producing naloxone-reversible (and thus presumably endorphin-mediated) analgesia.[30] Finally, naloxone can block the analgesia that results from consistently presenting an innocuous cue, such as a tone or light with a stressful pain.

Studies in humans, though somewhat complicated by the rich panoply of emotional and environmental factors that colors reports of subjective experiences, generally support the existence of an endorphin-mediated analgesia system. Although initial reports showed no effect of 0.4 to 10 mg of naloxone on experimentally induced pains, subsequent work has consistently shown that 10 mg of naloxone makes clinical pain worse. The studies on clinical pain compared the action of naloxone with that of a placebo and the worsening of pain with naloxone raised the possibility that the phenomenon of placebo analgesia might be accounted for by the action of this endorphin-mediated analgesia system. Subsequent work suggests that this is at least partly true. Our own studies of placebo analgesia show that stress, pain, environmental cues and expectation all activate the endorphin-mediated analgesia system.[31] Because of these complex factors and the possibility that placebo analgesia is endorphin mediated, early studies suggesting that acupuncture, transcutaneous electrical nerve stimulation and hypnosis all produce an opioid-mediated analgesia need to be reevaluated.

In summary, we have outlined the known properties of an endorphin-mediated analgesia system and have presented preliminary evidence that suggests that its

activation is part of a stress response and subject to complex environmental factors. In addition to the endorphins, there are other transmitter systems that play an important role in controlling pain transmission. The discovery of endorphin-mediated pain-modulating neural circuits has provided an explanation for how narcotic analgesics work and, perhaps more important, has greatly advanced our understanding of the variability of clinical pain.

The Management of Pain

In the following sections we will discuss the rationale for various methods in common use for pain management. Although treatment of the underlying disease should always be the primary goal, in many cases even when the cause is known, pain management is the major objective—for example, postoperative pain, labor pain or cancer pain. Because we cannot cover all methods of pain management in detail, we will focus on the optimal use of those therapeutic tools that are of greatest value for a broad range of physicians and discuss some general issues in pain management.

Behavioral Methods and Chronic Pain

Up to this point we have provided a very mechanistic description of the physiologic processes that result in the sensation of pain. The implication is that with this knowledge we should be able to achieve satisfactory control of pain in the overwhelming majority of patients. There are patients, however, who continue to complain of pain despite the use of potent analgesic drugs and repeated surgical treatments. Many patients with chronic low back or abdominal pain fall into this category and it would be misleading to discuss pain mechanisms and management without at least a brief discussion of recent developments in our knowledge of chronic pain.

Essential to an understanding of chronic pain is the distinction between the sensation of pain and the reaction or suffering aspect of pain.[19,32] The sensory aspect is usually studied by measuring pain threshold and is fairly uniform between human subjects. On the other hand, the subjective unpleasantness of or tolerance for pain varies greatly. A pain that one person would hardly notice would cause another to seek medical help. A simple way of thinking about this is that the sensory level (intensity) required for detection (pain threshold) is rather constant, whereas the intensity level required to elicit spontaneous complaints (tolerance "threshold") is highly variable.

For many acute pains such as occur during labor or following trauma or myocardial infarction, the pain intensity may well be above tolerance and lead to grimaces, groans, tears, splinting immobility and desperate calls for help. In addition to these overt behaviors, on physical examination there are often signs of increased sympathetic discharge such as a rapid pulse, increased blood pressure and sweating. These acute pains respond well to adequate doses of narcotic analgesics and need not pose a management problem

On the other hand, many pains that are less severe initially, such as in some cases of arthritis, headaches and back pain, become clinically significant simply because of their chronicity—that is, they are distracting, irritating and eventually depressing. Patients with these latter types of problems rarely groan, cry or show any of the usual sympathetic discharge that patients with acute severe pain do. They will, nonetheless, show up at clinics and hospital emergency rooms claiming that they have unbearable pain.

Until recently, most physicians have had great difficulty managing patients with subacute or chronic pain. Unable to cure the underlying disease—or in some cases to diagnose it—and appropriately unwilling to use potent narcotic analgesics on a long-term basis for nonmalignant disease, physicians tend either to dismiss these patients as crocks or to tell them they must "learn to live with the problem" without telling them how to do it.

In response to a growing awareness of this class of patients, a new approach to treatment has been developed, the behaviorally oriented, multidisciplinary pain clinic. These pain clinics tend to emphasize psychological, behavioral and physical rather than pharmacologic or surgical approaches.[33,34] Among the methods in common use are hypnosis, psychotherapy, biofeedback and behavioral modification techniques. Heat, ice, massage, physical therapy and transcutaneous electrical nerve stimulation are also used. What seems to distinguish successful pain management programs is that they tend to be patient oriented rather than disease oriented.

While not denying that a patient may have a "real" or an "organic" pathologic process that initially triggered the pain, these behaviorally oriented programs recognize that there are environmental factors that tend to reinforce illness behavior.[35] For example, a patient may have suffered an acute low back strain and have been put to bed, staying home from work for several days and receiving attention and sympathy or reprieve from responsibilities at work or at home. A prescription for tranquilizers or powerful opiate drugs, or both, may also have been given. Furthermore, people become more supportive, understanding and concerned about a person when he or she is ill. In short, being sick or at least having a valid complaint suggesting significant illness may have both primary and secondary gains for a patient. These rewards constitute reinforcement for illness behavior. Behavioral programs attempt to disconnect the illness behavior from the reward system by making patients more responsible for their own care and rewarding "normal" behavior such as increased activity or reduced drug intake. The goals include a return to productive life (which is something that can be verified objectively) rather than total elimination of pain.

Transcutaneous Electrical Nerve Stimulation

Although the therapeutic indications for transcutaneous electrical nerve stimulation (TENS) remain to

be fully spelled out, it is in common use in pain clinics and by physical therapists, neurologists, orthopedic surgeons and, in some centers, by general surgeons for postoperative pain.[36]

Because large-diameter myelinated axons have lower electrical thresholds than do small-diameter axons and do not produce pain when activated, it is possible to stimulate them selectively without producing discomfort. The earliest reports, on small groups of patients, indicated that TENS can produce dramatic relief of pain. These studies provide the impetus for larger clinical trials that have generally confirmed the usefulness of this approach.

The most carefully designed clinical trials, which have been carried out in patients with postoperative pain, show that TENS produces significant pain relief. It is routinely used for postoperative pain in some hospitals. Because postoperative pain has a consistent natural history and responds predictably to narcotic analgesics, these studies are all the more important. The evidence that TENS is effective in the treatment of chronic pain is not good; there are reports, however, of dramatic results in patients with pain syndromes associated with nerve damage. In these patients, TENS is most effective when stimulation is applied to the injured nerve proximal to the site of injury, where one can be assured of stimulating intact large-diameter axons. Recently encouraging results using TENS in the management of pain following spinal cord injury have also been reported.

This form of therapy is attractive because it is noninvasive, selective for pain and has few side effects. Its use requires detailed instruction, however, and patients will commonly have to experiment to find the most effective electrode positions. Thus, good cooperation is necessary for outpatient use.

Psychotropic Drugs

There is increasing evidence that psychotropic drugs have a place in pain management. Obviously, patients receiving psychotropic drugs could clinically improve for a variety of reasons. For example, pain that is a manifestation of depression would be expected to fade when the depression is relieved. However, there is evidence that certain psychotropic drugs may produce analgesia by acting directly on pain-modulation systems.

The most useful group of psychotropic drugs presently used in pain management is the tricyclic antidepressants. The effectiveness of tricyclics may relate to their actions in the central nervous system on biogenic amines such as serotonin (5-hydroxytryptamine) and norepinephrine. As mentioned above, both serotonin and norepinephrine-containing neurons form integral links in the endorphin-mediated analgesia system. Because tricyclic antidepressants, especially the methylated forms (imipramine, amitriptyline and doxepin), block serotonin reuptake, they would be expected to enhance its actions. Studies in animals have shown that tricyclics can produce "analgesia" directly or by enhancing the action of opiates.[37,38] Thus, there are good theoretical and experimental reasons for expecting clinical pain relief from this class of drugs. In controlled studies, tricyclics have ameliorated tension and migraine headaches.[39,40] In patients with postherpetic neuralgia, amitriptyline hydrochloride has had a pain-relieving effect that is rapid in onset and independent of relief of depression.[41] There are also anecdotes of its effectiveness in a variety of patients with chronic pain.

Phenothiazines are the other major class of psychotropic drugs that are used in pain management, usually as adjuncts to narcotic analgesics. Careful studies have shown that these drugs have little if any analgesic action either alone or in combination with opiates.[42] There is some evidence, however, that phenothiazines are useful when combined with tricyclic drugs in managing neuropathic pain.

Opiate Analgesia

Opium derivatives have been used for centuries to provide pain relief and remain the most potent analgesics available. Despite the long history of their use by physicians, it is well documented that patients, especially women and children, are often inadequately treated with narcotic analgesics.[43,44] This is due to several factors, including a physician's or nurse's fear that the patient will become addicted and a lack of knowledge of either appropriate dose or time course of the drugs' effects. Another source of difficulty is that the dose of a narcotic analgesic required to produce adequate pain relief varies greatly between patients[45] and the therapeutic endpoint is subjective. Thus, to assure adequate analgesia, additional doses must be given until a patient either reports relief or has unacceptable respiratory depression or sedation. Such a therapeutic approach requires that the patient be asked directly if the analgesic drug was effective. Unfortunately, this is often not done.

The finding of opiate receptors located in the dorsal horn of the spinal cord suggested that local application of opiates might produce a local analgesia without the side effects seen when these drugs are systemically administered. In fact, morphine has been given either epidurally (2.0 to 5.0 mg) or intrathecally (0.5 to 10.0 mg) to many patients for postoperative, posttraumatic and labor pain.[46,47] These doses of opiates are highly effective and, when given intrathecally, may produce analgesia lasting up to 24 hours. More recently, implantable infusion pumps have been used to epidurally deliver a continuous infusion of morphine to patients with cancer pain in the lumbosacral region. Although tolerance does develop within weeks, these devices can provide reasonable pain relief in terminally ill patients who no longer respond to very high doses of morphine given systemically.[48] Although useful, intrathecal and epidural administration of opiates produces dose-related side effects such as pruritus, urinary retention, nausea and vomiting and late respiratory depression in a significant proportion of patients. For-

tunately, most of the side effects can be reversed by doses of the narcotic antagonist, naloxone, which does not reverse analgesia. Commercially available morphine or meperidine preparations are probably not safe for intrathecal use because of preservatives.

Another newly developed approach for opiate administration is the use of continuous *intravenous* infusion. This can produce effective analgesia without excessive risk. The general applicability of this technique is limited, however, by the fact that the dose required may vary over a period of a day, and for technical reasons it is difficult to change the infusion rate to meet changing drug requirements. An alternate approach, patient-controlled "on-demand" analgesia, has proved highly effective and has been associated with a decrease in side effects when compared with nurse or physician administration of drug.[49,50] Even in the most enlightened medical environment, a patient must request medication, be evaluated by nursing personnel and wait for the drug to be obtained, a sequence of events that might easily take half an hour. In studies with a bedside on-demand analgesia apparatus, patients regulate pain effectively with moderate dosage and, in the case of postoperative pain, decrease drug use over time. This type of administration of analgesics has been used in Europe for some time and is not that dissimilar to the oral outpatient use of narcotics in the United States. It is likely that machines for patient-controlled analgesia will be licensed and available in this country within a year.

A discussion of narcotics for chronic pain is often limited to their use in patients whose pain is associated with malignancy. They have, however, been used successfully for nonmalignant chronic pain of musculoskeletal origin. Guidelines for narcotics use in these conditions need more systematic formulation. Starting with weaker opiates such as codeine, it may be possible to control chronic pain for years on dosing regimens that are stable. Obviously, patients need to be informed about the risk of tolerance and addiction.

Recent studies of the factors affecting analgesic response to opiates suggest some preliminary guidelines for the clinical use of this important class of drugs in patient subgroups.[45] Middle-aged patients require smaller doses than younger patients and the elderly less than middle-aged patients. Patients who describe their pain as dull obtain more relief than those who describe it as sharp. Finally, pain originating from the abdomen requires less medication than thoracic or upper-extremity pain.

Another approach to therapy suggested by the discovery of endorphins is to use pharmacologic agents that prolong their action. For example, there are enkephalinases that rapidly degrade enkephalins. One such enkephalinase inhibitor, thiorphan, has been reported to produce analgesia.[51] Furthermore, enkephalin analogs have been synthesized that resist degradation and retain analgesic potency. At present, these compounds are experimental agents.

Opiates, along with NSAIAs, are the mainstay of management for severe pain. The recent advances in their routes of administration have extended their clinical applications, and recent discoveries about their mechanism of action suggest that further advances are forthcoming.

Nonsteroidal Anti-inflammatory Agents

Nonsteroidal anti-inflammatory agents (NSAIAs), including aspirin and acetaminophen, are the most commonly used analgesics. Although the new NSAIAs have altered dosing regimen and toxicity, direct evidence for greater efficacy of this class of drugs is scanty. In fact, the major impact of newer agents that need to be taken only once or twice a day may be better compliance. Another possibility is that they are more effective simply because they contain a higher and thus more effective dose. Although it is commonly done with aspirin, no other NSAIA has been systemically administered at doses that are near toxic levels.

Additional recent changes in the clinical use of NSAIAs are broadening our perspectives on their role in pain management. For example, the availability of preparations suitable for parenteral administration may allow NSAIAs to be used for the treatment of pain syndromes for which they have not previously been considered applicable because of gastrointestinal toxicity or because of the severity of the pain. Both renal and biliary colic have been treated in this manner with apparent good results.[52,53]

The effectiveness of parenteral administration of NSAIAs in these conditions, generally considered to be associated with severe pain, raises doubt about the traditional teaching that these agents are only effective for pain of mild to moderate severity. Although renal and biliary colic and dysmenorrhea often produce severe pain, the fact that the pain is associated with local inflammation makes them candidates for treatment with NSAIAs. In this case, it is the *mechanism* of the pain rather than its *severity* that makes NSAIAs effective analgesics.

In part because of their popularity, NSAIAs have been used in different combinations with other drugs that have not been found to have established analgesic efficacy. Combinations such as NSAIAs plus mild stimulants, sold as over-the-counter preparations, may owe part of their efficacy to a placebo response perhaps enhanced by psychoactive actions of compounds such as caffeine.

A final clinical area in which NSAIAs have recently been applied with remarkable success is in preventing postoperative pain. Prophylactic administration before a surgical procedure is associated with less pain and swelling and decreasing requirements for postoperative narcotic analgesics.[54] The success of this therapeutic regimen could have been predicted from the mechanism of action of NSAIAs. Trauma invariably produces inflammation via prostaglandin synthesis, which in turn sensitizes the peripheral terminals of nociceptive afferents.

In conclusion, a better understanding of the mechanisms of peripheral nociceptive transduction processes and of the NSAIAs provides a rationale for the optimal use of these analgesic agents and has extended their therapeutic use to a broader range of clinical conditions. As discussed earlier, the recent elucidation of the role of the lipoxygenase pathway of arachidonic acid metabolism in pain promises to provide additional insights into the peripheral mechanisms of nociception and the possibilities for new classes of analgesic agents.

Sympatholytic Therapy

A number of pain syndromes are associated with increases in sympathetic nervous system activity localized to the painful region.[55,56] That sympathetic nervous system activity is causally related to the pain associated with these diseases is suggested by the observation that the pain is often exacerbated by stressors that increase sympathetic tone, and is abolished by selective regional sympathetic blockade.[57]

A mechanism by which sympathetic nervous system activity could produce pain is suggested by recent physiologic studies of regenerating fibers in a region of peripheral nerve injury.[58-60] The neuroma that forms near the regenerating end of the nerve contains a predominance of small-diameter axons, including both nociceptive primary afferents and sympathetic efferents. The afferents show increased sensitivity to sympathetic activity and circulating catecholamines. The clinical relevance of these observations is dramatically illustrated in patients with causalgia and reflex sympathetic dystrophy, where sympathetic blockade can dramatically reduce the pain. More recently, sympathetic block induced by regional intravenous or intra-arterial injection of the catecholamine-depleting agents, guanethidine and reserpine, has been shown to significantly ameliorate causalgia, minor causalgia and other forms of reflex sympathetic dystrophy.[55-57] The duration of pain relief varies from hours to permanent termination of the condition.

Our knowledge about the central nervous system control of the autonomic nervous system and the relation of this to clinical pain is poor. There is evidence that activity in large-diameter sensory neurons inhibits the sympathetic nervous system at the level of the spinal cord.[61] Regenerating sensory fibers in a neuroma are spontaneously active and respond to innocuous mechanical stimuli and, as mentioned above, to sympathetic nervous system activity. The mechanical hypersensitivity and spontaneous activity in the small-diameter afferent fibers in the absence of the normal inhibitory effect of the larger fibers has been proposed as the cause of the excruciating burning pain and superficial hypersensitivity that is reported by many patients. The dramatic relief of this pain by TENS in some patients supports the idea that reduced large-fiber input contributes to the pain and that large-fiber inhibition of activity in the sympathetic nervous system contributes to the analgesic effect of TENS. Other commonly used therapies such as ice, vibration, massage or other physical manipulations may have a similar mechanism.

Despite the intriguing observations described above, it is not clear how the autonomic nervous system "normally" affects pain perception. In part this is due to the difficulties in determining what aspects of autonomic function are specific to pain. We hope the recently renewed interest in the association of autonomic function and pain will provide an impetus for further insight.

Summary and General Treatment Strategies

The major components of the neural networks relevant to pain transmission and modulation are outlined in Figure 3. After transduction in peripheral terminals, signals are relayed to the spinal cord by small-diameter primary afferents. In the spinal cord, this signal is modified by simultaneously arriving inhibitory input from large-diameter primary afferents that have been activated by nonpainful stimuli. The pain message is then relayed by dorsal horn neurons to thalamocortical circuits, either directly or via the brain-stem reticular formation.

The pain-transmission system is continually modified by networks running from cortex to spinal dorsal horn. This modulatory system has both endorphin and biogenic amine links active at several brain levels. It is activated by pain, stress and a variety of other poorly understood environmental factors.

Given this complex system with its numerous neuronal links for transmission and modulation, it is clear that there are many possible sites at which the perception of pain can be altered. The two general approaches that have been used clinically are to either reduce transmission or to enhance modulation.

The two most commonly used classes of analgesic agents are the NSAIAs, which reduce transmission by interfering with the transduction mechanism at the peripheral receptor, and narcotics, which powerfully activate the modulating system by an action in the central nervous system. Because their mechanisms of producing analgesia are different, combining these two classes of drug to enhance analgesia has a strong rationale. On the other hand, the use of more than one drug within each class makes little sense.

Other major methods of blocking transmission include applying local anesthetic to peripheral nerve or spinal cord, giving narcotic analgesics epidurally or intrathecally and surgical lesions to interrupt the spinothalamic tract.

Sympathetic blocks and TENS make use of independent modulatory mechanisms. Sympathetic block reduces abnormal excitatory influences on peripheral nociceptors and TENS inhibits nociceptive transmission cells and, perhaps, sympathetic preganglionic fibers in the spinal cord. It should be possible to enhance sympatholytic therapy using catecholamine-depleting agents such as reserpine or guanethidine. These have been reported to work in some painful conditions

but only when given by regional perfusion in relatively high concentrations. Because TENS and sympathetic block work by unique mechanisms, their effects, if partial, should add to the analgesia produced by systemic drugs.

The descending pain-modulating networks can be activated by narcotic analgesics and, in some patients by suggestion (placebo) in the setting of significant pain and stress. It is also possible that certain physical methods such as heat, massage, biofeedback and acupuncture function, at least in part, by activating or enhancing pain-modulating networks.

Another therapeutic approach using pain-modulating networks is to enhance their nonopioid links. For example, there is experimental evidence that tricyclic antidepressants enhance opiate analgesia by potentiating biogenic amine links in the endorphin circuit. Thus, opiate-tricyclic combinations may be clinically useful. Opiate-tricyclic-NSAIA combinations might also have a place in treating patients who have an inflammatory component to their painful condition, if the pain is resistant to therapy with single drugs.

One of the major practical problems in managing pain is knowing when to refer patients for behaviorally or psychologically oriented treatments such as hypnosis, biofeedback, guided imagery, psychotherapy or a psychologically oriented inpatient program. Many patients are unwilling to take this approach, while more will find it an unsupportable financial burden. Physicians tend to use every medical option before requesting psychological referral. However, because chronic pain produces anxiety, depression and other emotional problems, it is useful to obtain psychiatric evaluation of these cases early. In some patients there will be a major psychological problem that is contributing to the intractability of the pain. In most cases, however, the contribution of psychological factors to the painful condition cannot be determined with certainty and an empiric approach, however unsatisfactory, must be taken. If some evidence of response to medical management or rehabilitation is not observed within a few weeks and the medical condition is stable, psychological evaluation and behavioral approaches to management should be considered.

One of the great challenges in pain management is to develop ways of evaluating the efficacy of behavioral therapies. Only then can we begin to define which patients will benefit. At present we must rely on anecdotal studies suggesting that pain clinics are helpful to patients with chronic pain.

In summary, in the past two decades there has been a remarkable expansion of our knowledge of pain mechanisms. Some of this progress has had an impact on patient care, but great challenges remain. Because pain is subjective and subject to complex physiologic and psychological factors, its management requires patience and sensitivity. Despite this complexity, or in some cases because of it, therapeutic interventions are often dramatically successful and rewarding to both patients and physicians.

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Medical Staff Conference

What Is Extraordinary Life Support?

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR BAXTER:* *It was inevitable that the advances in our ability to sustain life should have forced us to face the question of when the advances should be used. Physicians find this question difficult in its own right. They find it all the more so when the decision may be scrutinized by others who are unrelated to the patient and uninvolved in the patient's care, but whose judgment may have profound consequences for the patient, the family and the physician. We are fortunate to have Dr Albert Jonsen, Professor of Ethics in Medicine and Chief of the Division of Biomedical Ethics in the Department of Medicine, available to review the guidelines that can be inferred from a series of legal decisions involving extraordinary life support.*

DR JONSEN:† Thank you, Dr Baxter. I begin with an apology. Every time I give a Medical Staff Conference I seem to be talking about terminating life support, dying and things of that sort. This is somewhat discouraging. I would like to point out that these are not the only subjects that ethicists discuss, though they seem to be constantly on our minds these days. This concern with ethical issues posed by dying patients has come about because medicine has become so successful. For instance, one of the great discoveries of the 20th century was the ability to provide exogenous insulin. The only ethical problem then was whether Jews who had diabetes should be treated with pork insulin. But other problems have gradually appeared because treatment with insulin proved so successful that elderly persons with diabetes, whose life had been prolonged, had all of the late complications of the disease. Now we have the immense problems caused by extensive microvascular disease and by the enormous costs of their treatment. For example, we now must provide renal dialysis on a massive scale to a large population of patients who otherwise would probably not have lived to old age. The initiation of multiple new therapeutic possibilities are indeed creating serious ethical problems. So, it is the success of medicine and the growing sophistication of medical science and therapeutic efficacy that lead to the problems I am going to discuss here. We talk about problems caused by the termination of life support because we know how to provide life support; the ethical problem is the extent of our obligation to do so.

I am going to approach this subject by reviewing a number of legal cases (see Table 1), for it is important for everyone who is involved in decisions about the care of the terminally ill to know the way in which the

TABLE 1.—*Landmark Cases of Decisions on Life Support*

1976	*Matter of Quinlan.* New Jersey Supreme Court. Authorized discontinuance of respiratory support for 21-year-old woman in permanent vegetative state.
1977	*Superintendent of Belchertown State School* vs *Saikewicz.* Massachusetts Supreme Court. Approved decision not to provide chemotherapy for 67-year-old retarded and institutionalized man with acute leukemia.
1978	*Matter of Dinnerstein.* Massachusetts Appeals Court. Upheld validity of "no code" order for 67-year-old woman with Alzheimer's disease.
1979	*Matter of Spring.* Massachusetts Supreme Court. Approved decision to stop dialysis for 77-year-old man with dementia.
1980	*Application of Eichner.* New York Appeals Court. Authorized discontinuance of respiratory support for 83-year-old man in persistent vegetative state.
1980	*Matter of Storar.* New York Court of Appeals. Refused to approve discontinuance of transfusion for 52-year-old retarded man with bladder cancer.
1983	*Matter of Colyer.* Washington Supreme Court. Upheld removal of respiratory support of 69-year-old woman in chronic vegetative state.
1983	*Barber and Nejdl* vs *Superior Court.* California Appeals Court. Refused to instate homicide charges against physicians who discontinued respiratory and nutritional support from 55-year-old man in permanent coma.

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law has developed. However, I am really interested in drawing several nonlegal lessons from these legal cases. The courts reflect the ethics of a society. They do not do this directly—the courts do not take polls to make their decisions—rather, they reflect them indirectly. Judges are part of the wider society and, in their decisions, particularly when problems are novel and without legal precedent, they must draw on the collective wisdom of their society. Therefore, in every instance the courts have expressed their reluctance to come to grips with the cases and their uncertainty as to how to deal with them. What you hear in most of the legal decisions is a judge saying something like, "I really don't know where I am going, but there is an issue of public importance here; the courts have to take a stance relative to that issue of public importance. I am talking now more as a citizen than as a judge." What is most important about these cases is that they eventually teach us a lesson about the ethics of the care of terminally ill patients. This is most vividly expressed in the case that is most in the minds of Californians—the recent case in Los Angeles in which two Kaiser-Permanente physicians were charged with murder. I will review that case with you, not for the law, but for the ethical lesson it teaches.

I am going to review a series of cases, one case a year since 1976. These are what the law calls the leading cases. As I review them, remember that these are the most important cases, the precedent-setting ones.

Matter of Quinlan

We all remember the first case because it had wide media exposure in 1976—the Karen Ann Quinlan case in New Jersey. Quinlan was brought to an emergency room in coma, apparently the result of a drug overdose. She was put on a respirator and, after a certain period of time, neurologists determined that her coma was permanent and irreversible. Her family decided that they wanted the respirator discontinued, and the matter was referred to a court. The court after lengthy hearings gave the authority for the removal of the respirator. Quinlan began to breathe spontaneously and continues to live today in a persistent vegetative condition. The court stated that the authority to remove the respirator was based on the evidence presented that Quinlan would never return to what the court called a "conscious and sapient state." The family had the right to make the decision to discontinue life support. The court also recommended the use of an ethics committee, the first time an ethics committee was mentioned by a court. That committee, however, was described as one that would verify the prognosis, and therefore it was not so much an ethics committee as a committee of specialists, primarily neurologists, who could say something significant about the relationship between that young woman's clinical condition at a point in time and her future possibilities. What the Quinlan case shows is that removal of a respirator is permitted when the patient is judged to be in permanent and irreversible coma and when the patient's family wishes it to be done.

Superintendent of Belchertown State School versus Saikewicz

The next year brought the case of Arnold Saikewicz, a 67-year-old man who had been institutionalized from earliest childhood in a state hospital for the mentally disabled. He was able to dress and feed himself, but he had no other training and functioned at a very low level of social interaction. At age 67 years, he was discovered to be suffering from acute myeloblastic leukemia. Medical evidence presented in the court at that time stated chemotherapy would possibly provide a 30% to a 50% chance of remission for 2 to 13 months. The superintendent of the school requested authority to decide whether or not to proceed with chemotherapy. The court granted that permission to the superintendent; there was no family in this case. Chemotherapy was not initiated and Arnold Saikewicz died within about two months. In its opinion the court made some extraordinarily interesting statements. It said, first of all, that the poor prognosis with or without treatment was the first matter that it considered crucial to a decision not to treat. The second important matter was that Mr Saikewicz, with his extreme retardation, would not be able to understand and appreciate why he was suffering the likely toxic effects of the treatment. The court insisted that the fact of his extreme retardation did not in itself deprive this person of treatment; retarded persons are as worthy of medical care as any other person. The court found the retardation a relevant issue insofar as it limited the patient's understanding of what was happening to him in this situation. Had he been able to understand, the court reflected, he might well have refused a toxic treatment for a condition with so poor a prognosis.

Matter of Dinnerstein

In the following year (1978), also in Massachusetts, there occurred the case of a 67-year-old woman named Shirley Dinnerstein who suffered from Alzheimer's disease and was profoundly demented. She also had various physical disorders, including some cardiac problems. When she was admitted to hospital the question arose whether or not a "no-code" order should be written. The Saikewicz court had suggested court review for decisions not to provide life-sustaining treatment. Therefore, physicians wondered whether they could write a no-code order without a court's permission. They went to the court, which responded, of course you can write a no-code order without the court's permission. The difference between Saikewicz and Dinnerstein is important. Arnold Saikewicz was an institutionalized person without family. Public policy dictates careful external legal review of decisions made in those cases. Mrs Dinnerstein was a woman with a caring and loving family who was in a private hospital under the care of her own physician. The court decided that the probability that Mrs Dinnerstein would never

return to a "normal functioning integrated condition" was sufficient justification not to provide cardiopulmonary resuscitation.

Matter of Spring

In 1979, there was the case of Mr Earle Spring, again in Massachusetts. Mr Spring was 78 years old, senile and suffering from end-stage renal disease. When the question arose whether to put him on renal dialysis, the physicians, who felt he should not be dialyzed, sought the opinion of the court. The court returned a decision that it was appropriate not to dialyze Mr Spring. Then it explained at length when it is or is not appropriate to come to a court. Again, the court insisted that for cases in which there is not some compromising issue, such as institutionalization, decisions can be made appropriately by the family and the physicians involved.

Application of Eichner (Fox)

In 1980 occurred the case of Brother Joseph Fox, an 83-year-old man who was a member of a Catholic religious order. He was admitted to hospital for repair of an inguinal hernia and suffered a cardiorespiratory arrest postoperatively. He was put on a respirator and after some days was judged to be in permanent and irreversible coma. His religious superior, Father Eichner, testified that Brother Fox had mentioned in the course of discussions with his confreres that he would never want to be like Karen Ann Quinlan. As you may know, the Quinlan family is also Catholic. There was a great deal of discussion in the Roman Catholic community at the time of the Quinlan case about what those of that faith would judge to be appropriate care. The judge considered that a statement by Brother Fox, when he was quite competent, was sound reason to discontinue the respirator, establishing that previously expressed wishes of a patient are important factors.

Matter of Storar

In 1980 the court in New York linked a second decision with the *Fox* decision. John Storar, a 52-year-old retarded man, suffered from bladder cancer with a prospect of only six months of life. He was receiving regular transfusions, a process that he found to be very distressing. His mother who was his legal guardian requested that transfusions be stopped. In this case, the court said the transfusions should continue regardless of the very poor prognosis for his primary disease. The court said the difference between *Storar* and *Fox,* which case it was deciding at the same time, was that we have no way of knowing what Storar would have wanted because his inability to express himself was almost total. In Brother Fox's case there was evidence of a seriously considered, previously expressed wish. The court decided this case by looking not at the prognosis, nor the condition of retardation, but rather at whether or not there was an expressed wish about treatment at any point in time. Also, it made a comparison between transfusion and feeding in that blood transfusion is like food: we would not discontinue feeding; therefore, we should not discontinue transfusion. Both are "ordinary" means of care. The case of *Storar* is the only one among this series of leading cases in which the court insisted on the continuance of treatment.

Matter of Colyer

In 1983, the *Colyer* case was decided in Washington State: a woman judged to be in a persistent vegetative condition was on a respirator. The request for discontinuance was made by the family; the court approved it and said there really is no need for it to review cases of this sort. The court again suggested the usefulness of an ethics committee.

Conroy Case

A case is pending in New Jersey. Miss Claire Conroy was a lady of very advanced age who had been in a nursing home for a number of years. She had no family other than a nephew who had been quite close to her during the last years of her life. She suffered from organic brain syndrome with serious mental deficits and was being fed by a nasogastric tube. The nephew requested that the tube be disconnected. A lower court approved and Mrs Conroy died. That case was appealed and is now being considered by the New Jersey Supreme Court.

Barber and Nejdl versus Superior Court (Herbert)

Now we come to the Herbert case in Los Angeles, which is the most instructive one from the point of view of the ethics of life support. Mr Clarence Herbert had undergone a surgical procedure for bowel obstruction. He recovered quite well and then returned to the hospital in good health for closure of the colostomy. He suffered a respiratory arrest after the operation, was put on a respirator and within several days was judged to be in persistent and irreversible coma. After a short period of time the family requested discontinuance of respiratory support. The physician and the surgeon in the case concurred and discontinued respiratory support. Like Quinlan, Mr Herbert began to breathe spontaneously. After about four days, the family requested that all life support, including intravenous nourishment, be stopped. The physicians agreed and discontinued intravenous feeding. Mr Herbert died soon afterwards. Then a most unusual event occurred: the district attorney brought a charge of murder. All of the previous cases of which I have spoken have been civil matters in which authority was sought for a decision. In this case, the matter brought a criminal action.

This was the first time in American legal history that a criminal charge for murder was brought against physicians acting within the range of their clinical judgment. It is a very important feature of this case. There is a misapprehension that there has been a trial; there has never been a trial and there will never be one. The appropriateness of the charges was reviewed by a lower court and after a long hearing the charges were dismissed. A second court reinstated the charges, con-

cluding that the statutory definition of homicide in California was met by the circumstances of the case. The state court of appeals then again dismissed the charges, stating that the homicide definition was, in fact, not met. The district attorney decided not to appeal that decision, and so the case is at an end. What is interesting about the Herbert case is the lesson that the court provides about the ethics and the philosophy relative to the treatment of persons in this condition.

Discussion

Let me call your attention to several things. First, in every legal case reported here, with the exception of that of *Storar,* the judgment not to provide life support has been upheld. Physicians often have the impression that the courts regularly reverse such judgments. They do not. Every case except that of *Storar* affirms the clinical judgment about the inappropriateness of life support. The conditions under which those decisions are made have the following features: First, there is a judgment about the medical futility of continuing. Second, there is something to be said about the condition of the patient; in most cases the patients are either in a persistent vegetative condition or in irreversible coma. Third, in all of these cases there is either family agreement or there is some evidence that the patient would have wished the decision be made in that way. In every one of these cases, then, we have an affirmation, not a negation, of a clinical decision not to continue.

In the Herbert case, the court reflected on this problem in an unusual way. The court had at hand a very interesting document called *Deciding to Forego Life-Sustaining Treatment.* It was produced by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. It is an extraordinarily important document. I was a member of that Commission, and naturally I have some pride in authorship. First of all, the document was compiled after extensive attempts to get opinions from the best thinkers in the field. We had philosophers, theologians, physicians, sociologists and lawyers write papers on the problem. We held public hearings and heard from people of all sides, including the people who are in favor of active euthanasia and people on the other side who are very firm about continuing life support until the very last moment. From that extensive consultation we compiled a document that explores almost every aspect of the problem. It does not settle all the issues, but it does provide the first comprehensive view of the ethics of life support. Because one of the witnesses in the Herbert case had been a consultant to the Commission, that document, then in draft form, was put into evidence and the court used it extensively in framing its opinion.

One important feature of the document has to do with the idea of ordinary and extraordinary means of care. The court, following the Commission's thinking, stated that in the past the idea of ordinary and extraordinary means of care has been used to distinguish those cases in which life support could be discontinued from those in which it must be maintained. It has been commonly said extraordinary means of care can be discontinued; ordinary means of care must be continued.

The Commission concluded that this traditional distinction is not very helpful as it is widely misunderstood. The most common misunderstanding relates the terms ordinary and extraordinary to the state of the art of any particular medical intervention. Consider, for example, blood transfusion. We would all say that blood transfusion is an ordinary means of care in modern medicine. Transfusion is done readily, we know when to do it, we know how to use it, we know how to manage any adverse effects and it is effective in reversing the effects of blood loss. This leads to the kind of statement made by the *Storar* court that a transfusion is as ordinary as feeding. If we were to go back to 1934, 1933 or 1930, we would say that blood transfusion was extraordinary. At that time hematologic science was not developed enough to understand the entire range of problems, blood typing was scientifically undeveloped, practically difficult and unreliable and the management of the adverse effects of inappropriate transfusion was extremely difficult. Blood was not easily available. So in the 1930s we would have said that transfusion was extraordinary. It became ordinary when World War II pressed us to solve those problems.

What then is extraordinary in modern medicine? Under that definition the only things we could call extraordinary would be things that are now commonly thought to be experimental. That is of little help because the interventions in question in decisions whether to forego life-sustaining treatment are rarely experimental. Therefore, the Commission suggested that the terms ordinary and extraordinary are not helpful and other terms should be used. Language does not solve problems, but it helps us formulate problems with greater clarity. The terms the Commission suggested were proportionate and disproportionate care. To quote a passage from *Deciding to Forego Life-Sustaining Treatment* (which the court in the *Herbert* case quoted),

> Proportionate treatment is that which in the view of the patient has at least a reasonable chance of providing benefits to the patients, which benefits outweigh the burdens attendant on the treatment. A treatment course only minimally painful or intrusive may be considered disproportionate to the potential benefits if the prognosis is virtually hopeless of any significant improvement. . . . We view the use of intravenous administration of nourishments and fluids under these circumstances as being the same as the use of the respirator or any other form of life support.

The reason why "proportionate" and "disproportionate" are more helpful terms than "ordinary" and "extraordinary" is that they do not refer to the state of the art, but to a relationship between the effect of a treatment on the one hand and the benefit to the patient on the other. For some strange reason, much of the literature in clinical medicine and in the ethics of clinical medicine has tended to collapse those two sides of

the relationship. There is almost an assumption that every treatment effect will be beneficial. For example, for a patient on a respirator, there will inevitably be certain treatment effects. The primary goal is to maintain blood gases at a level to assure suitable oxygenation. That is a treatment effect. We know how to do it, it is done readily and usually easily. The ethical question is, does that treatment effect constitute a benefit? That is the question to be raised in every case. How does one determine whether it is a benefit? The court does not go into an abstract definition. Rather, the court says that "in these circumstances" (in Mr Herbert's case), namely, in which a patient is in persistent and irreversible coma, there can be no benefit. Why? The court does not enter into extensive discussion. The next round of literature in my field will surely discuss this issue, but we can assume the following argument (drawn to some extent from the Commission's report): A benefit is something that affects a person; it is something that a person can appreciate.

Appreciation is essential to the definition of a benefit. It may not be an immediate appreciation, as, when we discipline a youngster for some misdeed, we say, "You'll appreciate this some day." We hope there is a relationship between the immediate dissatisfaction of being spanked and the eventual appreciation that "I learned a good lesson." So a benefit may exist even when there is no immediate appreciation, but we recognize that it is absurd to use the term benefit where there is not nor will there ever be any appreciation. Thus, we may think that in the case of a person who is in a persistently vegetative condition or permanent coma, there can be no appreciation. That is a presumption, of course; we do not really know, but from everything that we do know, it appears that the neocortex is the organ of appreciation. When it is extensively damaged, there can be no processing of external experience or, to the best of our knowledge, internal experience. It seems reasonable to say that any sort of treatment effect cannot be appreciated; therefore, there is no benefit. So we are providing effects, not benefits. The court then affirms, in agreement with a basic principle of medical ethics, that it is the purpose of medicine to provide benefits, not treatment effects. Therefore, if it is judged there can be no benefit, there is no longer any duty to continue to treat.

We now face the next question: How do we handle the idea of proportion in practical clinical settings? Sometimes it will be clear, but other times there will be genuine dispute. For example, there was an unsuccessful attempt on the part of a private citizen in Los Angeles (who happens to be a district attorney) to have the *Herbert* opinion decertified. A decertification is not a reversal but means that the Supreme Court orders the opinion not to be printed in the official record, and thus it does not set a precedent. The reason for the petition for decertification was that, in the petitioner's words, "The idea of proportion is amorphous and indistinct." I agree. The distinction calls attention to the important features of the decision, namely, the relationship. But it still leaves us with a variety of questions about how we are to define benefit. There is the ethical problem. If Karen Ann Quinlan is in a persistent vegetative condition and Mr Herbert is in a persistent coma, how do they differ from Mrs Colyer who has organic brain syndrome or Miss Conroy who is suffering from dementia but is still conscious and responsive? How do they differ from persons who are retarded or from persons who suffer from certain limited sorts of mental deficiency? Those questions have to be discussed and debated case by case. Similarly, what difference does it make that in one case there is a loving family, deeply concerned about the patient and participating in the decision and in another case there is no family, but a legal guardian, and in yet another case the patient is completely alone? What difference does it make that a clear expression of wishes has been made on the part of the patient as distinguished from cases in which there may have been some uncertain expression or vague comment about preferences? What are those particular differences and how are they to be weighed in judging the proportion? These are the questions that face us today.

It has been suggested that an ethics committee might be helpful. Ethics committees are not widely in existence; less than 20% of acute care hospitals had ethics committees two years ago. This institution has had an ethics committee for seven years. Suddenly my office is getting about a phone call a week from hospitals in this vicinity asking how to set up an ethics committee. If ethics committees become a regular part of our clinical management of these cases, they will look carefully at the proportion between treatment effects and benefits. A good physician should be an expert at assessing treatment effects. It takes a lot of thoughtful, concerned people to look carefully at the issue of whether or not there is benefit.

QUESTIONS AND ANSWERS

PHYSICIAN IN THE AUDIENCE: *There seems to be little question as to the authenticity of the family's concern in Mr Herbert's case. The family virtually camped in the room to be sure that one member of the family was with him around the clock. But suppose the family had questionable reasons for their interest in seeing that their relative was not treated; suppose he was not on friendly terms with his family; suppose he had a girlfriend and the family then said, "Look, we don't want you to provide this dramatic care." Would this change your interpretation of the case?*

DR JONSEN: Absolutely. Those are precisely the kinds of things that require a consultation. The family has no legal authority to make these decisions in the state of California. This surprises people. The family has no legal authority, even when their family member is incompetent, unless a judge actually grants a guardianship. Girlfriends have even less. Even though the family has no legal authority, there is a reasonable presumption that their opinion is important. You do have rather special sorts of problems, and those problems

must be carefully reviewed—that is, finding out who these people are, what role they are playing, whether or not they are self-interested or interested in the patient and what other concerns there may be, such as a financial concern, and so on. This is the kind of thing that an ethics committee ought to do. We have had cases like that here in which there was no clear picture of who the people interested in the patient were and what role they played. We have often delegated to the social work member of the committee the task of learning more background information about the people involved. The issues need to be specifically and carefully dealt with because the implications are very different.

PHYSICIAN IN THE AUDIENCE: *How does one handle situations in which the family disagrees with the physician's advocacy for the patient?*

DR JONSEN: There is a case pending in Washington in which there was an almost immediate decision for a no-code order to be written for a patient when the prognosis was not at all clear, as if everybody said, "Oh, well, we don't want Dad to suffer." He didn't, for he died soon after admission. A physician needs to be very clear about the diagnosis and prognosis, and a physician's advocacy should come primarily by clarifying those issues, describing the real situation to the family. One of the problems with that kind of advocacy is that it is often posed in terms of many options without any recommendation being made. This is a bad tactic. It is not so much advocacy as the presentation of a buffet to a person who is on a diet and who does not know how to make choices. Here the support of other people can be critical. Nurses, for example, are sometimes more important as interveners because they often know the family much better than the physician does, particularly in acute care teaching hospitals. It is rare for there to be such disagreement that it becomes necessary to go to the law to seek authorization for a decision to terminate a treatment that in the view of the physician is totally nonbeneficial.

The cases that I have reviewed here are precisely of that sort. However, despite the difficulty, sometimes tragedy, of these sorts of cases, reasonable decisions—ethically, medically and clinically sound—can be reached. If the interpersonal elements of these difficult cases are managed sensitively, they can be resolved, for the most part, without the intervention of the courts.

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Epitomes

Important Advances in Clinical Medicine

General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in general and family practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Chlamydia trachomatis Infections

DURING THE past decade, the importance of *Chlamydia trachomatis* as a human pathogen has become increasingly apparent. Although lacking the notoriety of *Neisseria gonorrhoeae, C trachomatis* is known to produce a similar spectrum of human illness and is now considered a major sexually transmitted pathogen in the United States. In fact, studies indicate that we are currently in the midst of a "*Chlamydia* epidemic."

Chlamydia trachomatis is an obligate, intracellular parasite that has been implicated in a wide spectrum of human infections. Genital chlamydial infections occurring in men include nongonococcal urethritis, epididymitis, lymphogranuloma venereum, proctitis and possibly Reiter's syndrome. In women *C trachomatis* has been implicated as a cause of pelvic inflammatory disease, acute urethral syndrome, mucopurulent cervicitis, bartholinitis, lymphogranuloma venereum, postpartum endometritis and perihepatitis (Fitz-Hugh-Curtis syndrome). Neonatal infections caused by *Chlamydia* include inclusion conjunctivitis and afebrile pneumonia. Finally, the leading cause of preventable blindness in the world, trachoma, is also due to this microorganism.

The most sensitive method of diagnosis remains the tissue-culture isolation of *C trachomatis*. This test, though, is generally available only in laboratories of referral hospitals or large public health departments. Direct cytologic techniques for identifying *Chlamydia*-infected cells lack the sensitivity required for clinical use. Serologic tests are generally not useful in diagnosing current chlamydial genital infections due to a high prevalence of antibody from previous infections; they are of value in diagnosing neonatal chlamydial pneumonia and lymphogranuloma venereum.

As a result of the lack of a convenient, accurate test for diagnosing *C trachomatis,* decisions regarding diagnosis or treatment are frequently made on the basis of the clinical features, the exclusion of other possible pathogens such as gonorrhea and tracing contacts of patients who have nongonococcal urethritis, nongonococcal pelvic inflammatory disease and mucopurulent cervicitis. In view of the estimate that from 10% to 20% of men and 40% of women with gonorrhea are coinfected with *Chlamydia,* consideration should be given to empirically treating these patients with an antibiotic regimen effective against *C trachomatis*. Effective regimens against *Chlamydia* include seven-day courses of tetracycline, 500 mg four times a day, doxycycline, 100 mg twice a day, and erythromycin, 500 mg four times a day.

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Human Insulin

OUR ABILITY to artificially synthesize the amino acid sequence of human insulin was first achieved in 1963. Due to the low yield and the impurity of the product, human insulin has not been synthesized by this method. Porcine and bovine insulins have been the mainstays of diabetic insulin therapy. A newly developed method of human insulin synthesis has led to licensure and marketing of this product for widespread clinical use.

By artificially splicing the plasmid specifying production of human insulin, *Escherichia coli* can become human insulin "factories." This is one of the first practical applications of recombinant DNA technology. Insulin produced by this method has been immunologically, chemically and physically identical to insulin produced by humans. This recombinant DNA human insulin shows no traces of *E coli* contamination nor of any other side products such as proinsulin.

The major theoretic advantage of human insulin is the diminishment or avoidance of antigenic reactions, both local and systemic. Although less common, the more serious systemic insulin reactions have been associated with clinical situations in which insulin usage has been intermittent and there was a known allergy to other materials such as penicillin. Human insulin (recombinant DNA) is not a panacea and can be antigenic when administered subcutaneously. Nevertheless, this new product should be useful in certain clinical situations.

Family physicians will encounter the need for the intermittent use of insulin in gestational diabetes and during physiologically stressful periods (such as in surgery and the intensive care unit) in cases of type II diabetes. Human insulin may be the first choice in these situations. Cases of newly diagnosed insulin-dependent diabetes may benefit from the use of human insulin, particularly if they have a strong history of multiple allergies. The incidence of lipoatrophy may be diminished. Costs for one vial of insulin at one pharmacy in metropolitan Los Angeles were as follows: human insulin, $18; purified porcine insulin, $11; bovine or porcine insulin, $8. In a recent review, no evidence was found to support the use of human insulin in patients currently using older insulin preparations without allergic reactions.

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Cost–Effectiveness of Antenatal Rh Factor Immunoprophylaxis

REDUCING THE SEVERITY of Rh factor immunization, once it has occurred, is difficult. More effective by far is preventing the development of Rh factor immunization by administering Rh immune globulin. First licensed for clinical use in North America in 1968, Rh immune globulin injection will probably always prevent Rh factor immunization if given in an adequate dose before Rh factor immunization has taken place. The standard dose for prophylaxis is 300 μg. Smaller doses have been almost as effective. In England and Australia, for example, the doses are 100 μg and 125 μg, respectively. However, 300 μg of Rh immune globulin will protect a greater number of the women who occasionally have large transplacental hemorrhages.

In 1981 the American College of Obstetricians and Gynecologists reviewed protocols directed at further decreasing the frequency of Rh factor immunization by the use of Rh immune globulin in the following cases: prophylactically during the antepartum period; after amniocentesis; after antepartum hemorrhage and fetal death; after postpartum and postabortional sterilization; after transfusion of platelet concentrates and granulocytes, and in an Rh-negative, unimmunized woman (whether D^u positive or D^u negative) after delivery of an Rh-positive or D^u-positive infant. The most frequent reason for apparent postpartum failure of prophylaxis is most likely Rh factor immunization during pregnancy.

The cost-effectiveness of antepartum prophylaxis remains to be established. Treatment with Rh immune globulin at delivery only is very cost-effective. However, the addition of antenatal treatment where postpartum treatment is already routine is much less cost-effective. Furthermore, it is less cost-effective to limit treatment to women with homozygous Rh-positive husbands than to treat all women or all those with Rh-positive husbands. The possible savings by not treating women with Rh-negative fetuses is outweighed by the added costs of blood typing. Critics have also cited the increased requirements for Rh immune globulin, which may put hyperimmune Rh plasma donors at increased risk, as another disadvantage of antenatal prophylaxis.

There has already been considerable progress in reducing the incidence of Rh immunization. Routine antenatal Rh factor immunoprophylaxis is effective in further decreasing the rate of Rh factor isoimmunization by pregnancy, but greatly increases the demand for Rh immune globulin. It is appropriately done where Rh immune globulin supplies are adequate for all other needs, and cases of erythroblastosis fetalis still occur that might have been prevented by antenatal treatment. If antepartum prophylaxis is used, current recommendations are for the administration of 300 μg of Rh immune globulin at 28 weeks' gestation in an unimmunized, Rh-negative woman. Another 300-μg dose should be given after delivery of an Rh-positive or D^u-positive baby.

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Preventing Advanced Colorectal Cancer—Fecal Occult Blood Testing

RECENTLY THE American Cancer Society has initiated a three-year educational effort to change the way physicians and the public view the disease of colorectal cancer. The Colorectal Health Check (CHEC) Program will emphasize the expanded use of three standard diagnostic techniques for the early detection of colorectal carcinoma in asymptomatic patients. These tech-

niques consist of testing for occult blood in a stool specimen, rectal examination and sigmoidoscopy.

To obtain a reasonable predictive value, proponents of fecal occult blood testing have recommended certain conditions, which have included the dietary deletion of red meat, vitamin C, peroxidase-rich vegetables and nonsteroidal anti-inflammatory medications. Some have recommended adding a high fiber content to the diet during the test period. Storing stool specimens for longer than four days increases the percentage of false-negatives. Rehydration of slides is no longer recommended because of the increased number of false-positives.

Even with these refinements, there have been critics of stool guaiac screening in asymptomatic patients. The American Cancer Society currently recommends two specimens from each of three separate bowel movements, with adherence to the dietary and storage restrictions. Two studies published in 1983 have reported that most colorectal carcinomas detected by stool guaiac testing were at Dukes' stage A or B. These figures are dramatic deviations from commonly reported prevalences of from 25% to 50% for these prognostically more favorable stages of the disease.

Sontag and co-workers found that 71% of cases of cancer detected by stool guaiac were Dukes' stage A or B. A nonscreened comparison group diagnosed during the same period were found to have advanced (Dukes' C or D) disease in 75% of the cases. Hardcastle and colleagues used a prospective randomized design. In the group accepting fecal occult blood testing, 91% (11 of 12) of cases of diagnosed colorectal carcinoma was diagnosed at stage A or B. In the year following the screening period, ten cases of colorectal carcinoma were diagnosed in the control group. Of these, 60% were stages C and D.

These studies support the American Cancer Society's screening recommendations for fecal occult blood. New developments include vegetable peroxidase inactivators by Helena Laboratories and Coloscreen pads. These may assist clinicians by diminishing the number of false-negatives and improving patient compliance. Available products and their costs have been recently reviewed.

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Anorexia Nervosa

THE *Diagnostic and Statistical Manual of Mental Disorders,* 3rd Edition, (DSM III) includes anorexia nervosa as one of the "eating disorders," along with bulimia, pica, rumination disorder of infancy and atypical eating disorder. Of these, anorexia nervosa has received greatest attention recently in the lay press. It is a disorder that is associated with dysfunction at the physiologic, psychologic, familial and social levels. Recent studies have provided new information on anorexia nervosa; that from family studies is particularly intriguing in regard to the development of treatment regimens.

It is estimated that as many as 1 in 250 young women between the high-risk ages of 12 and 18 years suffer from this disorder. Cases occur in both younger and older women; less than 5% of cases occur in men. Diagnostic criteria for anorexia nervosa include an intense fear of obesity unrelated to actual body habitus, disturbance of body image, weight loss of 25% or more of original or projected weight, refusal or inability to maintain body weight and an absence of any physical illness that might otherwise account for the symptoms. Most cases occur in women from middle- to upper-class families. Families of affected persons have been described as caricatures of "perfectly normal" families; members may be unaware of chronic emotional withdrawal and isolation. Minuchin and co-workers refer to these families as "psychosomatic families" and describe them as having the characteristics of enmeshment, overprotectiveness, rigidity and an inability to tolerate or resolve conflict. Advocates of family systems approaches comment on the central and regulatory role the anorectic symptoms play in the family.

Treatment of anorexia nervosa is contingent on recognition. Management should be by physicians willing to commit themselves to involvement in a complex, difficult and sometimes frustrating disorder. Clinical approaches must be based on a certainty, shared by clinicians and family members, that weight loss beyond a medically determined level will result in admission to hospital, despite resistances encountered from the patient or her family. Tube feeding, not innocuous, is occasionally required. Physicians must insure that they are not deceived by the ruses of patients. Psychiatrists or family systems-oriented therapists with experience in the management of this disorder should be involved as early as possible. Families and individuals are often strikingly resistant to change; resolving the problem frequently involves uncovering previously denied family pathology and successfully dealing with it. Treatment and support may be required on a long-term basis. Primary care physicians and therapists must communicate openly and regularly; this is especially critical in the early months of care. As gains are made in patient weight and family function, contacts for support may be carefully spaced; physicians must recognize the potential for both early and late recurrence and for the emergence of psychosomatic problems in other family members.

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Computer-Assisted Reminders in Primary Care

It is no great surprise that computer-assisted reminders work. That they appear to work better than human memory-assisted systems is also no surprise. How much better and in which ways they have been shown to work may surprise some and interest others.

Computer-assisted appointment reminders reduced the no-show rate from 24% to 14% in a recent study at a university primary care center. Computer-generated reminder letters were cost effective if the no-show rate was above 5%, whereas telephoned or manual letter reminders, both of which cost about twice as much as computer-generated reminder letters, were estimated to be cost effective when the no-show rate was above 11%.

Computer-generated reminders to providers of certain screening, diagnostic and therapeutic maneuvers were more effective in changing the providers' level of compliance with the protocol guidelines than were no reminders. The reminders enhanced preventive care usage twofold in the study group, an important effect because the disparity between intent and action was greater in controls in preventive areas than in diagnostic and therapeutic areas. Computer-assisted physician reminders are more effective in enhancing the level of compliance with accepted intended actions than in initiating new but not yet accepted actions.

Computer-assisted reminders to patients enhance patient compliance with preventive services. Studies of computer-assisted patient reminders of immunizations in children and Papanicolaou smears in adults have shown significant enhancement in compliance with recommended guidelines. These findings are particularly important when one considers that the persons in whom invasive cervical cancer is most likely to develop, for example, are also the least likely to have been adequately screened and more often than not have seen a provider within the screening interval but have not had a Pap test done. The Centers for Disease Control now support the use of reminder systems for immunizations, and the Canadian Task Force supports their use for any "recognized preventive medical procedure."

Computer-assisted reminders have other roles in enhancing compliance, patient education, continuing medical education, quality assurance and research, to mention a few. They can improve patient care as long as that which we remind providers and patients to do is carefully shown to be safe and effective and is accepted before the reminders attempt to change behavior.

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The New Cephalosporins

Most clinicians familiar with the use of cefazolin sodium would anticipate the development of similar β-lactam compounds. Although many new compounds have been developed, none of them are yet the drug of choice for any disease. Indeed, the third-generation cephalosporin, such as cefoperazone sodium and moxalactam disodium, have less breadth than cefazolin and, generally speaking, are no more effective than the older, cheaper, first-generation compounds. The third-generation drugs are uniquely useful, however, against the group of Gram-negative rods that includes indole-positive *Proteus, Enterobacter, Citrobacter, Acinetobacter, Providencia, Morganella* and *Serratia.* Even among these bacteria, resistance is a problem, especially with *Enterobacter.* The only commonly accepted indications for the new cephalosporins are (1) Gram-negative rod meningitis, (2) rapidly worsening renal failure, (3) Gram-negative rod infections requiring prolonged therapy, (4) Gram-negative rod infections in which greater activity may be useful such as with a foreign body, (5) undrainable abscesses and (6) Gram-negative rod pneumonia. Third-generation cephalosporins have no place in surgery prophylaxis, specific Gram-positive infections (especially staphylococcal), community-acquired pneumonias or outpatient urinary tract infections.

Adverse reactions due to these agents are similar to those in older cephalosporins. Potential problems include emergence of multiple resistances (due to derepression of a gene coding for tightly binding β-lactamase), the development of superinfections (especially by *Candida* and enterococci) and bleeding due to hypoprothrombinemia (correctable with administration of vitamin K, 10 mg per week). One new toxic effect seen with moxalactam and cefoperazone is acute alcohol intolerance due to the inhibition of acetaldehyde dehydrogenase. Cross-reactions in penicillin-allergic patients have not been reported.

None of the new cephalosporins are superior to cefoxitin (a second-generation product) against anaerobic species, and all are much less active than clindamycin or metronidazole.

Cases wherein the third-generation cephalosporins represent a major advance are (1) *Escherichia coli* or *Klebsiella* meningitis (that is, moxalactam and cefotaximc sodium are superior to chloramphenicol or intrathecally given aminoglycosides), (2) second-line treatment of penicillinase-producing *Neisseria gonorrhoeae* infections and (3) nonneutropenic bacteremia in patients in whom resistance is a problem and *Pseudomonas* is not a consideration.

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AIDS—A New Epidemic

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) is a disease characterized by the occurrence of unusual neoplasms, chiefly Kaposi's sarcoma, and opportunistic infections, usually *Pneumocystis carinii* pneumonia. It was first recognized in June 1981 in six previously healthy homosexual men, and by April 1984 some 3,954 cases had been reported to the Centers for Disease Control, affecting homosexual men, intravenous drug abusers and Haitians both in and outside Haiti. Other groups affected include persons with hemophilia and other transfusion recipients, female sexual partners of men with the disease and infants from high-risk households. The ultimate mortality is unknown, but may approach 100%.

AIDS is defined empirically as the occurrence of infections and malignant lesions characteristic of an immunologic deficiency in the absence of any other cause of immunodeficiency. Basic science and clinical study of the disease has been hampered by the lack of a specific diagnostic marker. The classic syndrome commonly begins with *P carinii* pneumonia manifested by cough, chest discomfort and mild fever for two to ten weeks, accompanied by weight loss and diarrhea with or without enteric pathogens. Oral *Candida,* primary or recurrent herpes simplex and disseminated cytomegalovirus and Epstein-Barr viruses are frequently seen. Other opportunistic infections may also be found.

Two types of malignancy are seen with AIDS: Kaposi's sarcoma occurs in about 35% of patients, is commonly disseminated and usually presents as blue or brown nodules or plaques, usually on the legs; Burkitt's or immunoblastic lymphomas occur less frequently.

In addition, there is a syndrome of chronic lymphadenopathy, defined as three months' duration involving two or more extrainguinal sites with reactive hyperplasia on the lymph node biopsy specimen in the absence of illness or drugs that might cause lymphadenopathy. It is not clear if this represents a prodrome of AIDS or an entirely different syndrome, but in many who have it, classic AIDS develops.

Lymphopenia may be present, and T-cell subset analysis shows a decreased helper-suppressor cell ratio. Additionally, there is polyclonal B-cell activation with increased levels of serum immunoglobulin and abnormalities in the serologic response to a new antigen.

The cause of AIDS is yet unknown, but epidemiologic data suggest a single agent transmitted in a manner like hepatitis B, with an incubation period of about 18 months. Recent virologic and immunologic studies have shown the presence of human T lymphotrophic retroviruses (HTLV III) in a large percentage of those who have AIDS. Further studies are needed before causality can be determined or an immunization developed.

AIDS is clearly spread by sexual contact and via bloodborne transmission. There is no evidence that it is transmitted through casual contact. It appears to be concentrated in the United States, largely in major cities on both coasts, but is also seen in Europe, Haiti and Africa. The number of new cases is doubling every six months, and though about 3% of cases belong to a no-known-risk group, it is unknown whether the epidemic will extend into the general population.

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Premenstrual Syndrome

PREMENSTRUAL SYNDROME has become a popular topic in the lay press over the past few years, and it also has a growing medical literature. Because it is common (20% of women of childbearing age) and because treatment relies heavily on a good doctor-patient relationship, this disorder is well suited for treatment by a family practitioner.

Premenstrual syndrome is defined as an array of somatic and psychologic symptoms that occur during the luteal phase of the menstrual cycle and disappear sometime during menses. The symptoms are variable in occurrence and severity, but are significant enough to cause temporary incapacitation.

Common somatic symptoms are bloating, breast pain or tenderness, edema, skin rashes, hot flushes, headache, pelvic pain and change in bowel habits. Common psychological symptoms are irritability, aggression, tension, anxiety, depression, lethargy, insomnia, change in appetite, crying, change in libido, thirst, loss of concentration and poor coordination.

Diagnosing the disorder is dependent on a careful history. A diary of somatic and psychological symptoms during the menstrual cycle is essential for careful diagnosis. Three common patterns of symptoms occur. Some patients have problems during the week before menstruation whereas others become symptomatic starting at ovulation and are affected for two weeks. Others experience a few days of symptoms at the time of ovulation, with recurrence during the week before the menses. The symptoms generally disappear by the second day of menses.

Patient education and reassurance are the most important aspects of therapy. Many women find relief with an understanding of the condition and with reassurance that they are not suffering from a mental illness. General measures that may be helpful are regular exercise and a low-salt, low-carbohydrate (especially simple sugars), high-protein diet. Discontinuation of nicotine and caffeine is also advisable.

Pyridoxine hydrochloride (vitamin B_6) in dosages of 200 mg to 800 mg daily is generally the first choice

of drug therapy for this condition and is often effective. Dosages in this range are safe, and patients should be counseled to avoid higher doses that might cause a peripheral neuropathy. Spironolactone, 25 mg two to four times a day, has recently gained in popularity, especially in women with significant edema. Progesterone suppositories, 200 mg to 400 mg twice a day (may be used vaginally or rectally) beginning 10 to 14 days before menses, is a popular form of treatment. The Food and Drug Administration has not approved progesterone for treatment of this disorder and the cost is about $1 to $2 per suppository. Since no pharmaceutical manufacturers in the United States produce this suppository, physicians must find a pharmacy that is willing to formulate them. Taking synthetic progestins by mouth has not been effective and may actually make the symptoms worse.

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Outpatient Management of Diabetes

RECENT DEVELOPMENTS in the treatment of diabetes mellitus have dramatically improved the ability of primary care physicians to manage these patients. Although conflicting opinions still exist regarding whether or not tight control of blood glucose diminishes the risk of the microvascular complications of diabetes developing, most authorities believe that the available data suggest that patients and physicians should strive for the tightest control possible, without subjecting a patient to hypoglycemia. Ideally, we should strive in nonpregnant patients for fasting blood glucose levels of 140 mg per dl or below, and postprandial levels below 200 mg per dl. Also, the glycosylated hemoglobin level—a widely available test that reflects a patient's glucose control over a period of several weeks—should be kept as close to normal as possible.

Over the past years the dietary recommendations for persons who have diabetes have changed. Weight reduction is stressed for those who are overweight and is the first line of therapy for those with type II (non-insulin-dependent) diabetes. Complex carbohydrates are not restricted; in fact, they may constitute up to 60% of the daily caloric intake. Cholesterol, saturated fat and sodium intake should be reduced. Increasing intake of dietary fiber also improves glucose control.

Outpatient monitoring of glucose is changing dramatically. Recent studies have shown a very poor correlation between urine glucose and blood glucose levels. Home blood glucose monitoring using reagent strips, with or without reflectance meters, is much more accurate and is gaining in acceptance. Automated lancets have removed much of the discomfort of bloodletting.

Although some controversy about the oral hypoglycemic agents still exists, few believe that their risks are as great as suggested by the University Group Diabetes Program data. Nonetheless, oral agents are used only in cases of type II diabetes when diet alone has failed and, if possible, are avoided in patients with cardiac, hepatic or renal disease.

New, highly purified insulins are available, including human insulin of recombinant DNA origin. Patients with insulin-dependent diabetes currently doing well with the older products need not be switched. Patients beginning insulin therapy, however, might do well to start with human insulin or a highly purified porcine insulin—in theory, diminishing the risk of future allergic complications.

Finally, intensive regimens consisting of multiple subcutaneous injections a day or continuous insulin pump infusion will provide better glucose control than conventional regimens and should be considered for all cases of type I (insulin-dependent) diabetes. Although some deaths have been attributed to the use of the insulin pump, the death rate is not greater than the age-specific death rate for this population.

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Editorials

There Has to Be a God Somewhere

ELSEWHERE in this issue are two articles that discuss the present ethical, philosophic and legal status of either beginning or terminating what is being referred to (without really defining it) as extraordinary life support. The problem is who will decide whether someone should be allowed to die, let us say naturally, when the chances of survival or quality of life are slim. It was not too long ago that a family's physician could advise that "auntie" had lived a good life and that her "time had come," and that there was nothing more to be done except to make her comfortable. This was usually accepted by all concerned, often with some relief since the doctor had made the hard decision for them. But then it became possible to do more for persons in what had formerly appeared to be a hopeless or terminal condition. Physicians who had practiced as just described were accused of playing God—that is, of making life and death decisions more or less on their own. Indeed they had, albeit always in what they perceived as the best interest of the patient and family.

But what once may have been a largely private affair among doctor, patient and family, has now gone public—that is, it is being subjected to public scrutiny —and it is not yet clear where the role of God is to be played, if anywhere. It is now widely held that a patient should have the most to say about the use of extraordinary life support for his or her own person when able to do so. But it is not so often pointed out that by insisting that everything be done to preserve or prolong his or her own life, a patient may unfairly command the use of scarce resources needed by others and engender substantial costs that then must be paid by someone else. And who is to decide? Who is to play God here? Then if a patient is unconscious or incompetent, there is much attention now being paid to what someone else (a guardian, a family or perhaps a court) thinks the patient would have wanted done in the given circumstances—a difficult or almost impossible thing to ascertain unless, of course, someone is empowered by law to play the role of God in this instance. The so-called "living will," the California Natural Death Act and California's Durable Power of Attorney for Health Care are examples of efforts to strengthen the role a patient can play in determining his or her use of extraordinary life support should this become necessary. The well-known court cases discussed in these two papers describe the legal thickets that are created as judges wrestle with whether to or how to play God in these difficult situations. It is clear that neither legislation nor case law has yet dealt adequately with what should be the public's role in these very hard decisions in patient care.

The President's Commission for the Study of Ethical Problems in Medicine and in Biomedical and Behavioral Research produced the document "Deciding to Forego Life Sustaining Treatment." It raises the issue of what is extraordinary in modern medicine and notes that the distinction between what is ordinary and extraordinary treatment is blurred in modern patient care. It asks whether the proposed treatment is "proportionate or disproportionate" in terms of benefits to be gained versus the burdens caused. As suggested by Dr Jonsen in this month's Medical Staff Conference, we may now expect more discussion of what is a benefit and what is a burden and what is proportionate or disproportionate in any given case. Since these too will all be matters of judgment, it is hard not to believe that somewhere someone will have to play God and make these individual life and death judgmental decisions, unless somehow the God becomes an impersonal rule of law.

The two articles in this issue tell us where we are now with this complex problem, but they do not answer the question "Where is the God who in the final analysis must decide each case?" Things being the way they are, physicians may be thankful they are being relieved of this responsibility, except to offer their expert professional advice and opinion to whoever in the end must play God. But it seems that there has to be a God somewhere.

MSMW

More Terrible Than Death

We must all die. But if I can save him from days of torture, that is what I feel is my great and ever new privilege. Pain is a more terrible lord of Mankind than even death itself.

Thus did the great humanitarian Albert Schweitzer elegantly characterize pain and what he perceived to be his role in effectively relieving it. Certainly, the relief of pain has always been one of the most important reasons for the existence of physicians and, even today, one of our most important raisons d'être. Ample comprehension of pain and its mechanisms and the proper application of therapeutic modalities currently available are essential to the proper management of patients with acute and chronic pain.

Fields and Levine in their Medical Progress article, "Pain—Mechanisms and Management," present an excellent, concise overview of current concepts of the anatomic, physiologic and biochemical substrates of pain mechanisms and pain modulation and brief discussions of some therapeutic modalities that can be

used for pain relief. A very important point they make is that acute and chronic pain are different in regard to mechanisms and symptoms and in the approach to diagnosis and therapy. Another important aspect of the presentation is their focus on the changes in concepts regarding the clinical application of some forms of therapies, and the development of new ones as a result of recently acquired scientific information.

The value and relevance of this paper to clinicians are underscored by the fact that today, as in the past, proper management of patients with acute and chronic pain, including cancer pain, remains one of the most important and pressing issues of the health care system of this nation and other developed countries.[1] This importance stems from the fact that acute and chronic pain that requires therapy by physicians and other health professionals afflicts millions of people, and a significant number of patients with acute pain, and many with chronic pain, are inadequately managed. Consequently, pain is the most frequent cause of suffering and disability and seriously impairs the quality of life of millions of people. In most patients with arthritis, headache, neuralgia and other chronic painful conditions, it is *not* the underlying pathology but the pain that is usually the primary factor that impairs a patient's ability to carry on a productive life.

Although statistics from comprehensive national epidemiologic studies are not available, data from a number of local and regional surveys on various acute and chronic painful disorders suggest that annually pain afflicts nearly half of the American population. Of the 90 million Americans with chronic pain, some 55 to 60 million are partially or totally disabled for periods of days, weeks and months and some permanently. This results in the loss of more than 700 million workdays, which this year, together with the costs of health care services, compensation and litigation, totals $60 to $65 billion.[1,2] Consequently, pain in general—and chronic pain in particular—is a serious national economic problem and a major health problem.

There is impressive evidence that in the recent past, a large percentage of patients with postoperative pain, posttraumatic pain, severe pain associated with acute myocardial infarction, acute pancreatitis and other acute visceral disease—and most patients with postburn pain—have been inadequately relieved.[3-5] Moreover, many patients with nonneoplastic chronic pain have not responded to the usual medical therapy and impressive numbers have been exposed to the high risks of iatrogenic complications including drug toxicity, drug dependence and multiple, often useless, at times mutilating, operations.[1,6] A significant number of these patients have given up on medical care and have consulted quacks who not only have depleted their economic resources, but at times have done harm. Some patients with severe, intractable chronic pain have become so desperate as to contemplate or actually commit suicide. Patients with cancer pain have fared no better, and indeed there are numerous reports indicating that many patients with advanced cancer have lived the last months of their lives with unrelieved severe pain.[7]

There are many reasons for these serious deficiencies. For one, until two decades ago, the amount of research on pain and its mechanisms was meager and most of the small number of scientists involved were not concerned with clinical pain. This was especially true of chronic pain states, because most scientists did not appreciate the differences between acute and chronic pain. Moreover, the widespread assumption that pain was a purely sensory experience achieved via a simple, straightforward neural system caused emotional and psychologic factors to be relegated secondary roles, or as by-products of the sensation. This and other factors discouraged psychologists and behavioral scientists from being involved in pain research. Consequently, the crucial role of psychologic and environmental factors in causing chronic pain behavior had not been defined. Other deficiencies included the lack of national epidemiologic studies and the meager funds spent on pain research, even by the most affluent countries in the world. Thus we note that for the period 1971 to 1974, the National Institutes of Health spent about 0.03% of its annual budget to support research on pain mechanisms.[1]

Improper application of available therapies is an even more important reason for past deficiencies in pain control because we do have a variety of drugs and other procedures that, if properly applied, could provide effective relief. Several studies have shown that many physicians prescribe narcotics at two thirds of the doses required to relieve severe pain, and that nurses underadminister drugs by one third.[3,4] These studies show that the health professionals involved have an inadequate knowledge of the pharmacology of narcotics and consequently underestimate their effective dose range, overestimate their duration of action and have misconceptions about the potential for addiction and physical dependence. Moreover, some physicians do not appreciate that a number of other therapeutic modalities that could be used alone, or in conjunction with narcotics, might provide more effective pain relief. The blame for these deficiencies should not be placed on physicians and nurses, but must be assumed by medical and nursing schools, most of which do not provide effective and clinically relevant courses in the basic principles of managing acute and chronic pain. Moreover, the *symptomatic* treatment of pain is usually neglected in textbooks and journals: a review of 16 standard textbooks on medicine, surgery and oncology published in this country showed that of a total of 22,000 pages, only 52 pages are devoted to a description of the symptomatic treatment of severe acute or cancer pain.[1,8] In addition to inadequate diffusion of information, there has also been poor communication between investigators and clinicians, and consequently there has been a great lag in the clinical application of new information.

Fortunately, during the past two decades some developments have taken place that, if sustained and ex-

panded, hold out the promise of helping to rectify some of the above deficiencies. One of these has been the recent surge of interest and major efforts in pain research by a number of basic and clinical scientists and, in their collaborations with practitioners, efforts to begin to solve some of the major clinical pain problems. Fields, one of the authors of the article, has been in the forefront, both as scientist and clinician, and, in collaboration with Basbaum, Levine and others, has made critically important contributions to various aspects of pain research and therapy.

As pointed out in the article, during the past two decades we have acquired a great deal of new information that has greatly enhanced our knowledge of sensory coding and sensory modulation and has brought about a significant change in our perceptions of clinical pain and pain treatment. One important issue discussed by Fields and Levine is the recent psychologic and behavioral studies that have provided impressive evidence that the medical model does not adequately explain the abnormal illness behavior manifested by some patients with chronic pain, and that the inclusion of a behavioral model of pain is necessary. This emphasis that chronic pain behavior results primarily from reinforcing environmental influences, or so-called operant mechanisms, is long overdue and has had a favorable impact on the management of a number of patients with chronic pain. However, while this mechanism is responsible for chronic pain behavior in some patients, they represent only a fraction of the chronic pain population. In most patients who have arthritis, cancer, neuralgia, reflex sympathetic dystrophy and a host of other chronic pain syndromes, the persistent pain complaint is not the result of learning, but rather is caused by a persistent dysfunction of the nociceptive system.

In addition to the new and exciting developments mentioned by Fields and Levine, there have been significant advances in a number of other areas of pain research and therapy.[2] Some of these include (1) development and clinical trial of a large number of other cognitive and cognitive-behavioral methods of pain control; (2) better methods of pain evaluation; (3) the development of animal models for chronic pain including that due to nerve injuries and deafferentation caused by nerve section, rhizotomy and even tooth pulp injury, and (4) vast improvements in communication and diffusion of information. Moreover, an ever-increasing number of physicians and other health professionals have shown interest in acquiring more knowledge about pain and its treatment. The new knowledge of the serious pathophysiologic impact of deafferentation on the central nervous system has prompted the virtual abandonment of such techniques as peripheral neurotomy, surgical or chemical spinal rhizotomy and open cordotomy.

It is hoped that the recent momentum of pain research and therapy will continue so that in the not-too-distant future we will be able to achieve more effective control of acute and chronic pain.

The proper management of patients with pain, through more precise scientific information and proper application of therapeutic modalities, remains an important objective and a most gratifying achievement for physicians and biomedical scientists.

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Medicare—Progressively Overburdened and Underfunded

THE PREDICTIONS of bankruptcy for the Medicare program seem very real—whether in 1990 or at some other time. The question is what to do about it. The search for scapegoats, whether they be the health care system in general or physicians in particular, is naive and will do nothing to solve the problem. Actually no one can really be faulted, unless it be the proponents of the program who in 1965 did not, or chose not to, peer very far into what might happen in the years ahead.

Since the Medicare program was enacted in 1965, a great deal has happened that may or may not have been predictable, and more is likely to happen. There have been significant add-ons to the program in the form of additional beneficiaries and new benefits, without provision for additional funding to cover these extra costs. Then there has been inflation, a proliferation of federal regulations in every aspect of health care and a virtual epidemic of tort actions that often result in what seem to be unduly massive judgments against physicians and others in the health care field. All of these in various ways have added to Medicare costs. But perhaps most important of all in adding to Medicare costs has been the extension of the life expectancy of Americans, which means that, as the years have passed, Medicare beneficiaries have remained in the program for increasingly longer periods. This is a direct result of the national investment in medical science and technology, and in improved access to care of good quality, over the past 40 years. The skills

and technology needed to accomplish this extension of life expectancy in the latter years of life have been costly, especially when added to other environmentally imposed related costs such as those just mentioned above. And there is certain to be more of all this for the foreseeable future.

Victor Fuchs, professor of economics at Stanford University, has noted that in 1935, when the age of eligibility for social security retirement benefits was set at 65, life expectancy at age 65 was about what it is now at age 72. He suggests that old age now be redefined to start at age 72. In many ways this might be an eminently sensible idea. It seems to ring true. It is simple and could be accomplished with the strokes of Congressional and Presidential pens (alas, except for the political and emotional hue and cry that would surely be raised). But realistically it would preserve the intent of Medicare, substantially reduce its costs and significantly add to its income in relation to benefits paid out. It would also recognize for the public the really great payoff we have received for our national investment in medicine and patient care, a payoff that has been a national objective for nearly four decades.

But could something like this ever happen? Yes, it could, but probably will not. In our system, institutional memories are short. Governments tend to respond to self-interest pressure groups and what they perceive to be public opinion. Too often they have difficulty thinking or planning beyond the next election—never more than a few years away. It is more likely that the Medicare program will continue to be progressively overburdened and progressively underfunded, and that its value to those it was designed to serve will progressively diminish. There are times when radical surgery can prolong life, and even quality of life. This could be one of those times for Medicare.

MSMW

Medical Workups Before Eye Operations

MANY HAVE DEPLORED "cookbook" medicine and rebel against "routine" protocols for the evaluation of patients or specific conditions. Nevertheless, standardization in the approach in health care is often useful and may be cost-effective. In the interesting article by Levinson on preoperative evaluations, elsewhere in this issue, the data and analysis by the author suggest that there is a well-founded basis for the routine preoperative evaluation for patients undergoing eye surgery in a general community hospital. This paper is welcome because of the unusual nature of the subject: an attempt to look at the cost-effectiveness of that medical workup. The author is to be commended for her efforts. She concludes that the relatively modest costs of an internal medicine consultation and ordering of laboratory tests, based on the consulting physicians' findings, are most reasonable, given the overall expense to the patient for the ophthalmologic procedure itself. It is difficult to take exception to an evaluation that costs an average of $150 and that may be beneficial to a number of patients, considering that the overall hospital stay costs many thousands of dollars.

One cannot translate the results of this study into general preoperative evaluations. Eye operations are certainly less stressful than abdominal or thoracic procedures, which are more common surgical procedures in patients older than 60 years. It would appear that many of these patients may not have had ongoing care by a primary care physician, such as an internist or family practitioner. This is not necessarily true for many older patients who have serious medical problems requiring a surgical procedure, and therefore this population might be somewhat skewed, representing a group of persons who are receiving relatively little ongoing medical care. Unfortunately, no information is made available about whether the patients in this study had private physicians.

While I agree that considerable benefit was derived from the evaluations, particularly with respect to the identification of "incidental conditions" and to the fine tuning of the patients with respect to problems such as electrolyte imbalance, rapid atrial fibrillation or anemia, it is not at all clear that these routine evaluations did in fact decrease morbidity and mortality.

Significant postoperative problems were noted in eight patients. Five had apparently been screened and found to be free from significant problems by the internist before operation. The problems that arose in the other three were not related to the preoperative "risk condition" except for the single patient who had rapid atrial fibrillation postoperatively. In addition, of the three patients with so-called life-threatening complications, *none* had a risk factor identified in the preoperative evaluation. Thus of the 11 patients with major perioperative or postoperative complications, only 1 was identified before the operation as being at high risk (atrial fibrillation), and in this patient the intervention by the internist was not enough to prevent the rapid ventricular response. Of course, one could argue that delaying operations in four patients and identifying other health problems justifies the use of internists in evaluating these patients. As Dr Levinson points out in her discussion, the preoperative setting is not the most appropriate situation for a general evaluation of a patient. The follow-up for patients who were found to have previously unknown abnormalities is not clear and therefore an intervention by the consultant may well have had no lasting impact on the health care for these patients.

I do not suggest that the 20% of patients with a risk condition identified preoperatively were not benefited by the consultation, laboratory tests and therapeutic interventions. One would hope that an ophthalmologist could have identified most of the serious surgical risk conditions without consultation by an internist. This certainly would include the patients with a significant arrhythmia, recent heart attack, syncopal episode or pulmonary embolism or hypokalemia.

In conclusion, I agree with Dr Levinson that the

evaluations were relatively cost effective, given the overall expense of the operative procedures. I also concur that routine interventions in eye surgery patients should be limited only to those persons older than 50. Greater cost-effectiveness could have been achieved if the ophthalmologists had called for consultation in only those patients with significant surgical risk, as identified by history or by laboratory evaluation. It would appear that the routine evaluations were of benefit to the ophthalmologists to help avoid complications, but it does emphasize the narrow focus of specialists in medicine, and one wonders if good common sense and attention to details might not be even more cost-effective than calling internists in routinely.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Cardiac Pacemakers

QUESTION:

What are the criteria or indications for the use of cardiac pacemakers?

OPINION:

In the opinion of the Scientific Advisory Panels on Chest Diseases, General Surgery and Internal Medicine, implantation of cardiac pacemakers is considered established medical practice for the following conditions:

- Acquired complete atrioventricular (AV) heart block with or without symptoms.
- Congenital complete heart block with symptoms or bradycardia, or both.
- Bifascicular or trifascicular block with syncope attributable to transient complete heart block after other causes of syncope are excluded.
- Second-degree AV heart block of Mobitz type II with symptoms attributable to intermittent complete heart block.
- Asymptomatic second-degree AV block of Mobitz type II.
- Substantial sinus bradycardia caused by long-term necessary drug treatment.
- Recurrent and refractory ventricular tachycardia.
- In patients recovering from acute myocardial infarction with temporary complete or Mobitz type II second-degree AV block.
- Second-degree AV heart block of Mobitz type I with significant symptoms due to resulting hemodynamic instability.

In addition to these indications, there are other conditions which may warrant implantation on an individually determined basis:

- Symptomatic sick sinus syndrome.
- Symptomatic carotid hypersensitivity syndrome.
- Selected asymptomatic patients with sick sinus syndrome (such as those with pauses longer than 3 or 4 seconds).
- Bradycardia-tachycardia syndromes.

Pacemaker implantation may be deemed necessary in many other unique circumstances not included in the above list. Such individually determined decisions to implant permanent pacemakers must also be presumed to be appropriate practice.

Case Reports

Shigellemia

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SHIGELLEMIA (bacteremia caused by *Shigella* spp) is known to possibly complicate shigellosis. However, it is generally held to be a rare event that may occur at any time during the infection. Our experience with three patients who had shigellemia prompted a review of published information on the subject. From our review, we conclude that shigellemia is not rare, it occurs in patterns and it has prognostic importance.

Patients and Methods

We reviewed the records of blood cultures processed in the clinical microbiology laboratories of the University of California, Davis, Medical Center (UCDMC) from March 1971 through December 1980 and the Sacramento Kaiser-Permanente Hospital (SKPH) from June 1973 through March 1980. In addition, the reports of shigellemia published after 1948 were analyzed by grouping patients according to several criteria: underlying medical problems, age, survival and timing of bacteremia in relation to the clinical onset of disease.

Patients in whom shigellemia occurred in the presence of severe nutritional deficiency, pneumonia, cirrhosis, hepatitis, sickle cell anemia or diabetes mellitus were considered to be abnormal hosts. If shigellemia was detected before or within 24 hours of the clinical onset of colitis, the bacteremia was classified as *early;* shigellemia detected more than 24 hours after the onset of colitis was classified as *late*. Reports with insufficient information to permit such classification were excluded from analysis. When appropriate, differences in rates of occurrence were evaluated for statistical significance using either the χ^2 test (with the Yates' correction) or Fisher's exact test.*

Reports of Cases

CASE 1. The patient, a 35-year-old paraplegic homosexual man, had the sudden onset of lower abdominal cramping pain associated with watery, frequent diarrhea. As the diarrhea continued, the feces became blood-streaked and his temperature, taken orally, rose to 40°C (104°F). He was admitted to UCDMC 24 hours after onset of symptoms. There was no known exposure to anyone with diarrhea, and he recalled no change in his diet. However, he had been the recipient in rectal coitus about 24 hours before his illness began. He was an experienced recipient and recalled neither rectal pain nor tenderness. He said he had not had oral copulation.

On examination, his temperature was 37.8°C (100°F), his pulse rate was 120 per minute and his blood pressure 130/60 mm of mercury; the left side of his abdomen was tender. Blood-streaked feces was obtained at rectal examination; a Gram-stained smear showed large numbers of leukocytes and a variety of bacteria. *Shigella sonnei* was isolated from cultures of a fecal specimen and a blood specimen (one of two sets taken 24 hours after onset of symptoms). There were 6,800 leukocytes per μl in a blood specimen taken on admission, with 2% mature and 31% band form neutrophils, 23% lymphocytes, 22% monocytes, 9% metamyelocytes and 13% plasmacytoid lymphocytes.

The initial treatment with nafcillin sodium (one day) was changed to ampicillin, 200 mg per kg a day given intravenously every four hours as six equal portions for four days, then 30 mg per kg a day given by mouth every six hours as four equal portions for six days. Recovery was uneventful.

CASE 2. Severe headache, fatigue and fever began suddenly in a 17-year-old boy. Cramping with low abdominal pain presaged the passage of a single, loose, nonbloody bowel movement. His temperature, taken orally, was 40°C (104°F). There was no known exposure to anyone with diarrhea. He was admitted to SKPH six hours after his illness began.

On physical examination, the patient's temperature was 39.8°C (103.7°F), the pulse rate was 120 and there was postural hypotension (115/60 mm of mercury, supine; 68/36 mm of mercury, standing); there was no abdominal tenderness. *S sonnei* was isolated from cultures of a fecal specimen and a blood specimen (in one of five sets taken seven hours after onset of symptoms). There were 12,800 leukocytes per μl in the blood on admission, with 84% mature and 9% band form neutrophils, 3% lymphocytes and 4% monocytes. The initial treatment with ampicillin (one day) was changed to trimethoprim-sulfamethoxazole by mouth, two tablets (320 mg and 1,600 mg, respectively) every six hours for ten days. Recovery was uneventful.

CASE 3. The patient, a 4-year-old Asian-Indian boy,

*David Feigal, MD, provided statistical analysis.

(Kligler RM, Hoeprich PD: Shigellemia. West J Med 1984 Sep; 141:375-378)

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had diarrhea and a temperature rising to 38.9°C (102°F) (oral). Other family members had similar illnesses. He was admitted to UCDMC 96 hours after his illness began with dehydration, acidosis and hyponatremia.

On examination, the rectal temperature was 37.7°C (99.8°F) and the pulse 128 (the blood pressure was not recorded). *Shigella flexneri* was isolated from cultures of a fecal specimen and a blood specimen obtained six days after onset of symptoms. The diarrhea persisted and the temperature increased to 40.4°C (104.8°F) on the third hospital day. There were 6,200 leukocytes per μl in a blood specimen taken on admission, with 5% mature and 44% band form neutrophils, 24% lymphocytes and 22% monocytes. Ampicillin was given intravenously in a dose of 150 mg per kg

TABLE 1.—*Reports of Shigellemia Grouped According to Species*

Study	*Number and Description of Cases*	*Outcomes*
	Shigella flexneri	
Henson, 1956[8]	1 normal child	Survived
Darasse, 1957[9]	1 child with kwashiorkor	Survived
Robertson, 1963[10]	3 normal children	Survived
Faucon and Duclous, 1964[11]	1 adult with hepatitis	Died
	1 normal adult	Survived
Spiller and Grant, 1966[12]	1 child with sickle cell anemia	Survived
Graber et al, 1966[13]	1 adult with diabetes mellitus	Died
Levin, 1967[14]	1 five-day-old neonate	Died
Kim and Hughes, 1968[15]	1 newborn	Died
Jackson and Kilgore, 1971[5]	1 nine-day-old neonate with meningitis	Died
Naveh and Friedman, 1973[16]	1 six-month-old infant	Survived
Kazal et al, 1976[17]	1 homosexual man with megacolon	Survived
Hallett and Scragg, 1978[2]	1 neonate	Survived
Scragg et al, 1978[3]	2 neonates	Died
	1 five-month old with kwashiorkor, pneumonia and typhoid	Died
	5 2-year-old children with pneumonia (4), kwashiorkor (2), marasmus (1)	All died
Phillips et al, 1979[18]	1 normal adult	Survived
De Mol et al, 1981[19]	2 normal children (5 and 33 months)	Survived
Cordle and Boltjes, 1963[20]	3 normal children	Survived
This study	1 normal child	Survived
	Shigella sonnei	
Henson, 1956[8]	1 child	Survived
Darasse, 1957[9]	1 adult with cirrhosis and ascites	Survived
Tatam et al, 1951[21]	1 child	Survived
Winter and Harding, 1962[22]	1 adult	Survived
Whitfield and Humphries, 1967[6]	1 neonate	Survived
Rubin et al, 1968[7]	1 child with sickle cell anemia and shigellal osteomyelitis	Survived
Kraybill and Controni, 1968[23]	1 neonate	Survived
Barrett-Connor and Connor, 1969[24]	3 normal children	Survived
Barrett-Connor and Connor, 1970[1]	1 normal child	Survived
Evans et al, 1972[25]	1 normal child	Survived
Fernhoff and Plotkin, 1973[26]	1 normal child	Survived
Moore, 1974[27]	1 neonate	Died
Spiers, 1974[28]	1 child with acute monocytic leukemia	Died
Neter et al, 1974[29]	1 adult postrenal transplant	Survived
Aldrich et al, 1979[4]	1 neonate	Died
Scragg et al, 1978[3]	25 children with pneumonia and marasmus	Survived
Lloret Caballeria et al, 1980[30]	1 neonate	Died
O'Connor and O'Callaghan, 1981[31]	1 adult with bone marrow aplasia and cecal perforation	Died
This study	2 normal adults	Survived
	Shigella dysenteriae	
Sodre et al, 1949[32]	1 normal child	Survived
	1 normal adult	Survived
Ullis and Rosenblatt, 1973[33]	1 normal child	Survived
Rahaman et al, 1974[34]	4 children, 3 with secondary hemolytic anemia	Unknown
Koshi et al, 1979[35]	6 children, 3 or 4 with marasmus, kwashiorkor and/or renal failure	All died
	Shigella boydii	
Barrett-Connor and Connor, 1969[36]	1 child with sickle cell anemia	Survived
	Multiple species and non-differentiable	
Hallett and Scragg, 1978[2]	22 cases, 17 *S flexneri*, 3 *S sonnei*, and 2 *S dysenteriae*. Except for 1 all had severe underlying malnutrition, pneumonia, typhoid and/or cirrhosis. 20 children younger than 2 years	8 died
	2 adults	1 died

of body weight a day as six equal portions every four hours for four days and then was given by mouth in a dose of 100 mg per kg a day (as four equal portions every six hours) for five days. Recovery was uneventful.

Results

As shown in Table 1, our three cases plus the 87 cases reported by others yield 90 cases of shigellemia documented since 1948.[1-36] Of these, 48 (53%) were caused by *S flexneri,* 26 (29%) by *S sonnei,* 15 (17%) by *Shigella dysenteriae* and 1 (1%) by *Shigella boydii.* The case death rates were 2 of 32 (6%) in patients who had no underlying abnormality ("normals"), 19 of 44 (43%) abnormal hosts and 8 of 12 (67%) neonates; ($P<.001$, comparing the abnormal hosts and the neonates with the normals using the χ^2 test with Yates' correction factor).

Through evaluation of those reports in which the timing or number (or both) of blood cultures was ascertainable, two patterns of shigellemia became apparent. With *S sonnei,* the bacteremia was detected during the first 24 hours of illness in 14 of 18 (78%) episodes, whereas with *S flexneri,* 20 of 24 (83%) episodes were detected after the first 24 hours of illness ($P<.001$ by Fisher's exact test). Only 1 of the 22 patients with *S sonnei* had two positive blood cultures, whereas 5 of the 37 patients with *S flexneri* had 11 separate blood cultures that yielded the shigellae (not a statistically significant difference by Fisher's exact test).

Discussion

The presumption of the rarity of shigellemia is based on several early reports of failure or infrequent identification of *Shigella* spp in blood specimens from patients proved to have shigellosis by culture of feces.[1,37-39] However, more recently 3.2% to 6.4% of cultures of blood specimens yielded *Shigella* spp.[2,3,40,41] This apparent discrepancy may be related to (1) the use of the wrong technique in culturing the blood, (2) inhibition of bloodborne *Shigella* spp by humoral antibodies and leukocytes, (3) failure to get a blood specimen at the proper time in the illness and (4) a change in the kind of patient now seen with shigellosis.

With regard to the first reason, it should be noted that *Shigella* spp are not fastidious in their nutritional requirements. However, controlled evaluations enabling definition of the optimal volume of blood to be added to a given volume of liquid culture medium have not been done and the relative nutritional adequacy of various formulations has not been determined.

The putative inhibitory effect of humoral antibodies and leukocytes on the outgrowth of bloodborne shigellae would be nullified by the additive sodium polyanethol sulfonate in culture mediums currently in use. This additive is an effective anticoagulant that also inactivates complement and leukocytes.[42] Such actions may be important in view of the demonstrated killing of shigellae in vitro by serum from humans containing IgM and complement—acting through either the classical or an alternate pathway.[43] The susceptibility of shigellae was unrelated to either the titer of antibody or prior exposure of the donor to *Shigella* spp. However, susceptibility to killing does vary considerably according to species and serotype, in order of increasing resistance: *S sonnei*=*S flexneri* 1; *S flexneri* 2; *S flexneri* 3.[43] This variation in susceptibility of *Shigella* to humoral defenses appears to correlate with the persistence of shigellemia.

It is clinically apparent that bacteremia caused by *S sonnei* is most likely to be detected during the first 24 hours of illness. Although this is the optimal time for detecting shigellemia, patients do not always seek medical attention during this period. Those who do see a physician are generally treated symptomatically and cultures are not done. If the disease persists or progresses, cultures of fecal specimens are usually done, but less frequently of a blood specimen. The result could be a skewing of the data toward a falsely low incidence of shigellemia and an apparently high mortality. In a prospective study of mildly to moderately severely ill patients, however, the incidence of shigellemia did not correlate with the severity of the disease.[40]

Immunocompromised and neonatal patients appear to be less able to confine *Shigella* spp to the intestine. As a consequence, their fatality rates are greatly increased, as is the probability of occurrences of extraenteric shigellosis, such as meningitis,[5,6,44] pyelonephritis,[44] osteomyelitis[7] and otitis media.[44] Because the detection of shigellemia in immunocompromised and neonatal patients appears to have grave prognostic importance, the blood should be cultured even when the illness appears to be trivial.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Thermally Mediated Wound Healing in the Anatidae

To the Editor: In my surgical practice, I strive to promote wound healing by paying strict attention to surgical principles proved over time. Such factors as meticulous technique, adequate blood supply, tension-free anastomoses, proper nutrition and the like are of undisputed importance. There is, however, an additional factor that has not received sufficient attention.

I have discovered a technique for optimal cosmesis in the closure of skin defects overlying the body cavity of domestic fowl. A continuous suture of 3-0 chromic catgut, under the influence of moderate oven temperature, yields a virtually invisible suture line. Knowledge of this technique is most significant during the months of November and December, when such repairs are commonly performed.

Suture removal is best effected after the surgeon has been premedicated with a good white wine.

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Cough Radiculopathy—Another Cause of Pain in the Neck

To the Editor: While cough can, at best, be considered an invaluable reflex, it can be responsible for a number of problems, including syncope, headache, vomiting, subconjunctival hemorrhage and urinary incontinence. We wish to report the phenomenon of cough radiculopathy as another cause of pain in the neck.

Report of a Case

Violent coughing developed in a 44-year-old steroid-dependent woman with asthma. This was associated with the abrupt onset of excruciating pain radiating down the right arm, accompanied by tingling and weakness. The paresthesias were located in the right third, fourth and fifth fingers. On examination, she was found to have decreased strength in wrist dorsiflexion, finger abduction and some weakness of arm extension. Sensory examination showed a loss over the dorsum of the fourth and fifth fingers of the right hand extending onto the forearms. Deep tendon reflexes were active and symmetric with the exception of the right triceps jerk, which was absent.

Despite conservative therapy with a cervical collar and a short course of high-dose steroids, there was no improvement. On a cervical myelogram (Figure 1) there was evidence of an extruded disc and C-7 root compression. A posterior laminectomy was carried out at C-7 with immediate pain relief and an uneventful subsequent course.

Discussion

Acute cervical radiculopathy is an uncommon condition that chiefly affects middle-aged persons.[1] Symptoms may be mimicked by neoplasms, cysts, rheumatoid arthritis, infections, apophyseal osteoarthrosis and degenerative disc disease with spondylosis. The diagnosis can be made with myelography, discography or a surgical procedure.[1] Conservative therapy with traction and analgesics is recommended initially. If an operation is required, several recent reports suggest that anterior cervical discectomy without fusion is the best approach.[2,3]

The cause of disc protrusion is controversial. Martin found that 49 (72%) of his 68 patients with lumbar

Figure 1.—Cervical myelogram with arrow marking the area of disc protrusion at C-7 level.

disc herniations had a history of trauma that varied from minimal to severe.[4] Most of these patients noted the sudden onset of back pain. Of the patients with no history of trauma, the onset of pain was typically gradual. In 3 of the 68 patients acute radiculopathy had developed when coughing or sneezing was added "to their other trauma at the time of onset."[4] In our patient, the herniation also developed suddenly in association with violent coughing. There was no history of other trauma. The patient had no pertinent history other than her chronic asthmatic bronchitis. Since she had not taken systemic corticosteroids for four months before the onset of the cervical disc herniation, their role, if any, is unknown. In addition, systemic corticosteroid therapy is not known to be a risk factor for cervical disc herniation.

In summary, this report documents an unusual complication of violent coughing, namely cervical disc herniation. It broadens the differential diagnosis of acute cervical radiculopathy.

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Use-Associated Problems With the Vaginal Contraceptive Sponge—A Preliminary Report

To the Editor: Although the vaginal contraceptive sponge has been marketed since July 1983, little information has been published on its effectiveness, safety and acceptability. Unpublished studies have been reported to show pregnancy rates of from 10 to 27 per 100 woman-years of sponge use.[1] Preliminary results of a study comparing the sponge with the diaphragm suggest that the sponge may not be as effective as the diaphragm, especially in women familiar with the use of vaginal contraceptives.[2]

Sponge-associated toxic shock syndrome has been documented on four occasions.[3] The first was in a woman who was 37 days postpartum, another in a woman who had difficulty removing the sponge, finally resulting in sponge fragmentation, the third in a woman who had left the sponge in for 32 hours and had trouble with removal, and the fourth in a woman who left the sponge in for five days. None of the women were menstruating and all were admitted to hospital and recovered.

In the study comparing the diaphragm with the sponge, sponge acceptability appeared to be high with only 1% to 2% of users experiencing difficulties with insertion, removal or vaginal discomfort.[2] No other information on the kinds or extent of use-associated problems has been reported. Because we had seen several patients with questions and concerns about the contraceptive sponge, we surveyed a group of sponge users about their experiences.

Methods

Female students using the San Diego State University Student Health Center from March through May 1984, indicating on their gynecologic history that they had used or were currently using the sponge, were asked to complete a one-page questionnaire. In addition, women purchasing the vaginal sponge at the Student Health Center Pharmacy were given the questionnaire and a stamped return envelope. Questions were completed anonymously and included questions about length of use of the sponge, reason for selection, previous methods of contraception, problems associated with its use and reasons for discontinuation if the sponge was no longer used.

Results

Thirty-six students responded, ranging in age from 18 to 29 years (median 21 years). Half (18) of the respondents indicated that they were still using the contraceptive sponge with an average length of time from first use of the sponge to completion of the questionnaire of 3.4 months. The half (18) indicating that they were no longer using the sponge had used it an average of 2.4 months.

Asked why they selected the sponge, the majority (24) indicated "convenience" as the reason. Others felt that the sponge held an advantage over the other barrier methods and spermicides because it was "less messy."

TABLE 1.—*Previous Methods of Contraception and Problems Experienced by Contraceptive Sponge Users**

	Continuing Use	*Discontinued Use*	*Total*
Other Birth Control Methods Used Previous to Use of the Sponge			
Diaphragm	10	6	16
Condom	8	8	16
Spermicides	5	4	9
Birth control pills	9	10	19
None	2	2	4
Problems Associated With Use of the Sponge			
Trouble inserting	..	5	5
Complaints from partner	2	4	6
Trouble removing	9	12	21
Increase in vaginal infections	1	4	5
Discomfort	2	3	5
Interferes with intercourse	..	1	1
Displacement	1	..	1
Odor	1	1	2
Pregnancy	..	1	1
Vaginal irritation	3	6	9
No problems	5	..	5

*36 respondents. One or more responses could be given by the same respondent.

Table 1 classifies the respondents by "continuing use"/"discontinued use" categories and lists the frequency of problems and the previous contraceptive experience of each group.

Discussion

Certainly, with only 36 respondents it is impossible to draw conclusions from these data. Students using a student health service are more likely to have a complaint, leaving those who are satisfied with the sponge and "problem-free" underrepresented.

These data suggest, however, that the frequency of problems associated with the contraceptive sponge may be higher than previously reported. Of particular concern is the large percentage of women who had trouble removing the sponge. If removal of the sponge is delayed, the risk of toxic shock syndrome may be increased.

Because the sponge is available over-the-counter without a prescription, it is important for all physicians treating patients who might be sponge users to be familiar with its benefits and risks. Experience in our population, though limited, indicates a relatively high likelihood of sponge-related problems.

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Allergy as a Cause of Recurrent Headaches

To the Editor: I find an urgent need to comment on the article "Headache—Diagnosis and Effective Management" by Dr K. S. Peters in the June 1984 issue.[1]

I have observed over the years that patients generally are at a serious disadvantage because specialists in fields other than clinical allergy fail to recognize allergic involvement in many conditions. I suggest that such specialists—and I include those who treat headaches—resemble the proverbial blind men examining their first elephant and describing the part they feel as the whole animal. Allergy is a systemic or constitutional condition that finds expression in many areas. Recurrent headache is one of these areas and the literature abounds with reports of headaches with clear specific relationships to allergens. Dr Peters does not refer to allergy as a cause of headache. Cluster headaches, mentioned by Dr Peters, have been reported by others as occurring in the spring or fall seasons yet the author fails to consider the allergic implications.

Each treatment suggested by Dr Peters is symptomatic. There is no therapeutic attention to etiology. The fact that it is possible to treat recurrent headaches from allergic causes effectively with relief of symptoms certainly suggests that the possibility be entertained and proper historical questioning be applied.

Dr Peters is not alone in his neglect of this important consideration. It is high time to correct such neglect.

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Nephrotic Syndrome Associated With Degenerating Uterine Leiomyoma

To the Editor: The nephrotic syndrome has been associated with a large number of possible etiologic factors including many infections and neoplasms.[1] Uterine leiomyomas have been associated with systemic manifestations.[2] To our knowledge the case presented below represents the first published case of nephrotic syndrome developing in association with a degenerating uterine leiomyoma.

Report of a Case

A 33-year-old woman (gravida 5, para 2 0 3 2) was admitted to the Oroville (California) Hospital and Medical Center with the complaint of severe right lower quadrant pain of 12 days' duration. Her last menstrual period was approximately one month before admission. She had had two abortions and one miscarriage, but none recently. Six years before admission she had been sterilized laparoscopically. Menstrual pattern had been normal. There was a five-year history of hypothyroidism, for which she was taking two grains of thyroid daily. She had had peripheral edema one month before, which resolved when she took diuretics given her by a friend. The pain of which she complained was initially so excruciating that the referring doctor considered a diagnosis of appendicitis.

On physical examination the uterus was noted to be enlarged to 12 weeks' size and was exquisitely tender on movement and direct palpation of the right parametrial area. Vital signs were initially within normal limits and she was afebrile except for one temperature of 37.8°C (100°F). Findings on examination were otherwise normal and specifically there was no peripheral edema. Analysis of urine showed proteinuria (4+); no abnormalities were noted on microscopic examination of urine except for a few leukocytes and rare granular casts. A 24-hour urine study showed protein loss of 22 grams. Serum total protein was 4.4 grams per dl with serum albumin value 2.1 grams per dl. Serum creatinine concentration was within normal limits and creatinine clearance was 149 ml per minute.

Hemoglobin was 14.3 grams per dl. Leukocyte count and differential were normal. Sedimentation rate, corrected, was 44 mm per hour and an antinuclear antibody study was positive with a speckled pattern to a

titer of 1:160. An antistreptolysin O titer and chorionic gonadotropin were nil. Free thyroxin index was 2.5 (normal 5.5 to 12.5). A sonogram confirmed the presence of a right-sided intramural mass and intravenous pyelogram was normal.

It was felt that the patient's nephrotic syndrome was related to the enlarged uterus. On the day following admission, under general anesthesia and through a Cherney incision, a total abdominal hysterectomy and bilateral residual salpingectomy, without oophorectomy, were carried out. Dilation and curettage, laparoscopy and, at the patient's request, perineorrhaphy were also done. The laparoscopy was done because the operating physician had not ruled out the possibility of a malignant condition of the ovaries, which would have required a different operative approach. Pathologic studies showed a large degenerating intramural fibroid (Figure 1). Renal biopsy was not done.

The patient had an uneventful postoperative course. On discharge urine reaction for protein was only 1+ and two weeks later 24-hour urine protein loss was only 446 mg per day. A brief report from the patient's current physician 20 months after discharge indicates that the patient is well and symptom free, with normal sedimentation rate and creatinine clearance, no proteinuria and a 1:20 speckled antinuclear antibody titer.

Comment

It is believed that the nephrotic syndrome is frequently due to immune complex deposition in the glomerular basement membrane,[3] which is very likely the mechanism in this case. No documented infection or signs of infection were found.

Presumably the immune complex was related to release of antigens from the degenerating leiomyoma. The rapid resolution of the nephrotic syndrome following the operation was striking and further supports the belief that the leiomyoma was the etiologic factor.

It is interesting that the radiologist who did the ultrasonography raised the possibility of a hydatidiform mole. This was not felt to be a probability because of the lack of any detectable chorionic gonadotropin. The possibility that a degenerating leiomyoma may mimic hydatidiform mole has been commented on elsewhere.[4]

This report adds to the long list of causes of nephrotic syndrome and may be of help in finding a treatable cause for nephrotic syndrome in patients with leiomyoma who are not as symptomatic as our patient.

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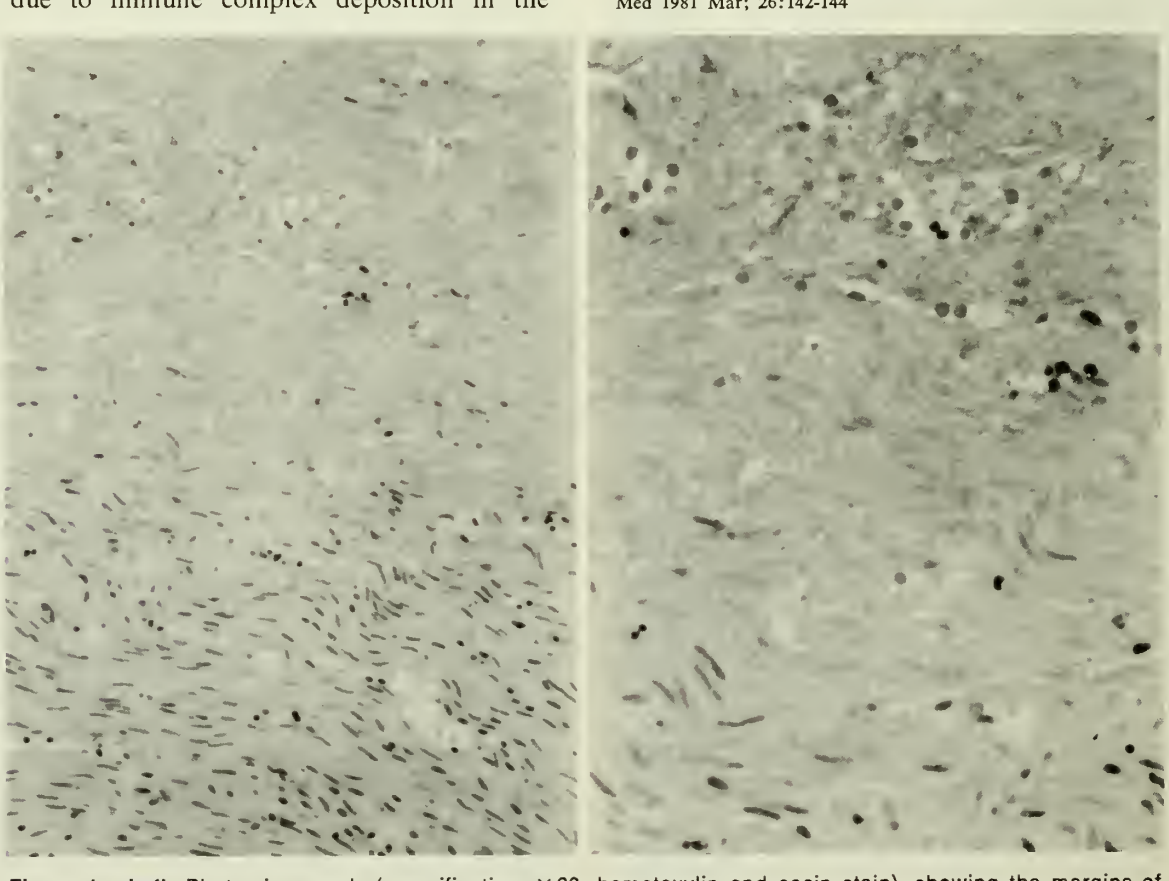

Figure 1.—Left, Photomicrograph (magnification ×60, hematoxylin and eosin stain), showing the margins of viable and nonviable muscle fibers. **Right,** Same specimen and same stain (magnification ×300).

Topics in Primary Care Medicine

Prescribing Exercise

LINN GOLDBERG, MD, *and* DIANE L. ELLIOT, MD, *Portland*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Regular physical exercise provides both physical and psychological benefits. Adaptations to training include increased oxygen use by the exercising muscles, decreased myocardial oxygen consumption for a given workload and thus improved work and exercise capabilities. Exercise also reduces cardiovascular risk factors (blood pressure and lipoproteins), aids in weight reduction, retards osteoporosis and is an important adjunct to physical rehabilitation. Psychological accompaniments of training result in reduced anxiety and depression and an enhanced sense of well-being.

As therapy, exercise has indications, contraindications and side effects. Following appropriate medical evaluation, an exercise prescription can be recommended that will give maximum benefit with minimal risk.

Preexercise Evaluation

Before exercise testing or conditioning, a careful history of the cardiovascular, pulmonary, metabolic and musculoskeletal systems is necessary. Information suggesting a history of a myocardial infarction, claudication or obstructive lung disease should be sought; any of these conditions can limit exercise performance and modify the exercise prescription. Musculoskeletal problems can prevent a patient from doing certain exercises, thus altering the type of activity prescribed. Assessing previous physical and occupational activities helps determine the present level of fitness and types of exercise enjoyed. Known cardiac risk factors such as hypertension, cigarette smoking, hyperlipidemia, diabetes and a family history of early coronary disease should be identified. Using oral contraceptive drugs adds additional cardiovascular risk to women who also smoke during their late childbearing years.

A medication history is essential for the interpretation of testing and monitoring an exercise program. For example, β-blockers reduce the resting heart rate and attenuate exercise limits. Substances with anticholinergic effects can alter temperature regulation and necessitate modification of training practices. Diabetic patients usually require a reduction of their insulin dosage to avoid exercise-induced hypoglycemia.

The pretraining physical examination should focus on the peripheral vascular and cardiopulmonary systems. Diminished arterial pulsations or the presence of a bruit often indicate peripheral vascular disease and alter training mode and capacity. Auscultatory findings of a third or fourth heart sound imply reduced ventricular compliance, whereas a systolic heart murmur can suggest either aortic stenosis or idiopathic hypertrophic cardiomyopathy (or subaortic stenosis [IHSS]). The latter entity is the most common cause of cardiovascular death in young adults during exercise. A prominent fourth heart sound is usually present in patients with IHSS. Simple clinical techniques that alter the ventricular volume assist in identifying this abnormality. They include an increased intensity of the murmur after Valsalva's maneuver or a reduction of its intensity when the lower extremities are raised. In addition, nearly all patients with hypertrophic cardiomyopathy have abnormalities on their resting electrocardiogram. If a clinician believes the murmur to be more than innocent, echocardiography is indicated to determine its cause.

Physical and laboratory variables should be assessed before exercise and followed throughout the course of

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ABBREVIATIONS USED IN TEXT
ECG = electrocardiogram
IHSS = idiopathic hypertrophic subaortic stenosis
Vo_2 max = maximal oxygen consumption

training. Changes in these measures can be used to follow the effects of the exercise program. Although underwater weighing is more precise, measuring skinfold thickness at several sites via skinfold calipers is a convenient method to quantitate body fat. Evaluating the alignment, stability and range of motion of the major joints allows for appropriate modification of the type of activity involved in training. Body strength can be approximated by measuring the maximal isometric handgrip with a dynamometer.

Laboratory investigation provides information pertaining to exercise functional capacity and predictors of cardiovascular disease. A hematocrit is determined to assess the potential oxygen-carrying capacity of a patient's blood. Serum glucose and cholesterol determinations assist in identifying persons with coronary risk factors. High-density-lipoprotein cholesterol levels should be done only in those patients who have hypercholesterolemia or a family history of early atherosclerosis. Triglyceride levels need not be routinely evaluated, as their value as a risk marker for coronary heart disease is still unclear. The serum potassium level should be measured in all patients taking diuretics because hypokalemia can lead to serious cardiac arrhythmias during exercise and render patients more susceptible to rhabdomyolysis. Depending on a particular person's history or signs, an electrocardiogram, chest radiograph and other laboratory tests may be done.

Exercise Testing

Graded exercise testing is useful in identifying risks to physical exertion, measuring functional capacity and establishing guidelines for training. The American College of Sports Medicine recommends exercise testing for all sedentary patients older than 35 years before beginning a conditioning program. We recommend graded exercise testing for men who are older than 35 years and relatively inactive. Because coronary artery disease is less prevalent in younger women, the predictive value of stress electrocardiography is considerably less among this group. Therefore, for women patients up to 45 years without a history of heart disease or other contraindications, we allow progressive training without prior exercise testing.

Many maximal exercise electrocardiographic (ECG) protocols using either a treadmill or a bicycle ergometer have been developed. Exercise testing should always include continuous ECG monitoring, resting and exercise heart rates, blood pressure determinations at various workloads and the maximum heart rate attained. Although not always reliable, the predicted maximum heart rate may be estimated by subtracting a patient's age from 220. Thus, a normal 40-year-old patient's maximum attainable heart rate would be about 180 beats per minute. This estimation should be substituted by the maximal level attained during stress testing.

During exercise ECG testing, the development of arrhythmias, horizontal or downsloping ST-segment depression of 1 mm or more or upsloping of the ST segment equal to or more than 1 mm 80 ms from the J point are electrocardiographic criteria suggestive of ischemic heart disease. Other ECG predictors of coronary artery disease include ST-segment elevation, R-wave voltage increase, serious ventricular arrhythmias occurring at low heart rates (120 to 130 beats per minute) and a reduced heart rate response to increasing exercise workloads. Symptoms of anginal pain add significance to the presence of ischemic-appearing ST segments during exercise. Blood pressure responses during exercise testing are also important; a reduction in blood pressure early in the testing protocol is often a sign of reduced cardiac output and severe coronary disease. In addition, increases in diastolic blood pressure and an inability to do three minutes of exercise are indicators of coronary atherosclerosis.

Interpretation of a positive test depends on both clinical and electrocardiographic findings. Besides coronary artery disease, ischemic-appearing electrocardiographic responses during stress testing can be the result of aortic stenosis, hypertension, left ventricular hypertrophy, anemia, hyperventilation or merely a variant of normal. A nonfasting state, hypokalemia and certain medications, such as digitalis, can also result in false-positive values. The predictive accuracy of stress testing for the diagnosis of coronary artery disease depends on the clinical presentation, age and gender of a patient. For example, a 45-year-old man with typical anginal chest pain and 2 mm of ST depression during exercise testing has a 98% probability of significant coronary disease. A similarly aged asymptomatic woman with the same ST depression has only a 10% likelihood of having coronary atherosclerosis. In asymptomatic persons, the predictive value of the graded exercise test for coronary heart disease increases when ischemic responses are noted at lower levels of exertion (stages I through III of the Bruce protocol) and at lower heart rates (below 160). Stress scintigraphy for perfusion defects or coronary arteriography (or both) can be used to evaluate cases of highly suspicious test results. A more complete strategy for evaluating a case of an asymptomatic patient with a positive test has recently been reviewed by Goldschlager. Additionally, exercise-related arrhythmias can be discovered during bicycle or treadmill testing, findings that will affect the intensity and duration of the exercise prescribed.

Besides the development of myocardial ischemia, graded exercise testing may be terminated because of dyspnea, dizziness, claudication or fatigue. The maximum attainable heart rate, limited by one of these symptoms, provides a guide for the intensity of training. Each patient's recommended level of physical activity can be determined and expressed as a percentage

of either their maximal attainable heart rate or of maximal oxygen consumption (Vo_2 max). Maximal oxygen uptake relates to one's maximal ability to transport oxygen to exercising muscles. This depends on the circulating erythrocyte mass, maximum cardiac output (maximum heart rate times maximum stroke volume) and maximum arteriovenous oxygen difference. Vo_2 max is affected by age (decreasing after age 18), habitual activity (regular exercise increases use) and gender (men's greater than women's after puberty). Direct measurement of Vo_2 max is not generally available, but relatively accurate estimations of maximal oxygen uptake in persons without heart disease are based on heart rate responses to imposed workloads. However, estimation of Vo_2 max by submaximal exercise testing in patients with cardiovascular disease can be unreliable.

Contraindications

Absolute and relative contraindications to exercise are listed in Table 1. Absolute contraindications include the presence of acute or unstable cardiovascular and infectious diseases.

Relative contraindications should be weighed against the diagnostic or therapeutic benefits of exercise testing and training. They include uncontrolled metabolic disease (hyperthyroidism, hypothyroidism or diabetes) and chronic illness (chronic renal, hepatic or musculoskeletal disease) that would inhibit the development of a training effect. Patients with frequent ventricular ectopic activity, supraventricular tachycardia, ventricular aneurysm, moderate hypertension or significant anemia have an increased risk of complications during physical exertion and should exercise only under medical supervision.

Exercise Prescription

An exercise prescription should include both the type of activity and guidelines for its intensity, duration and frequency. Based on the initial assessment, patients can be placed in one of the four following groups: (1) healthy, relatively young (men younger than age 35, women younger than age 45) with low cardiac risk; (2) apparently healthy, older patients (men older than age 35, women older than age 45) with a low cardiovascular risk profile and no abnormalities on exercise testing; (3) high risk for cardiac disease or abnormalities noted on graded exercise testing, and (4) established cardiac disease. Patients in groups 1 and 2 need only receive initial instruction and proceed to unsupervised training. Group 3 patients require initial supervision and may progress to unsupervised exercise after a reevaluation if training responses occur without complication. For patient safety, we believe group 4 patients should do exercise training only with appropriate supervision. However, because of economic and logistic constraints, those without severely depressed ventricular function, exercise-induced hypotension or complex ventricular arrhythmias can subsequently graduate to an unsupervised setting after a period of education and close monitoring.

TABLE 1.—*Contraindications to Exercise*

Absolute
Acute myocardial infarction (early)
Unstable angina pectoris
Active myocarditis
Dissecting aneurysm
Uncompensated congestive heart failure
Ventricular tachycardia and dysrhythmias
Severe aortic stenosis (valvular, supravalvular)
Severe hypertrophic cardiomyopathy
Thrombophlebitis
Recent pulmonary embolism
Acute infectious diseases
Severe systemic hypertension
Relative
Frequent ventricular ectopic activity
Supraventricular tachycardia
Ventricular aneurysm
Mild to moderate aortic stenosis
Mild to moderate hypertrophic cardiomyopathy
Anemia
Uncontrolled metabolic diseases (diabetes, myxedema, thyrotoxicosis)
Hypokalemia
Musculoskeletal disorders
Pulmonary hypertension

The type of exercise is determined by a patient's desires and needs. Aerobic fitness is primarily enhanced through continuous rhythmic endurance activities of large muscle groups, such as brisk walking, jogging, cycling and swimming. Swimming and cycling result in low levels of musculoskeletal stress and can be done by those who have particular orthopedic impairments. Persons who work with their arms will derive more benefit from upper extremity exercise because there is little carry-over in the training response to "untrained" muscle groups. Racquet sports and games usually have an inadequate duration of continuous activity to produce a cardiovascular effect.

The intensity of endurance exercise (energy cost per unit of time) is often based on the MET (metabolic equivalent unit) system in the cardiovascular laboratory, whereas the pulse rate provides a basis for clinical monitoring. A MET unit is the approximate amount of energy expended (oxygen consumption) at rest (3.5 ml of oxygen per kg per minute). An adequate training intensity for endurance conditioning usually requires a heart rate response of between 70% and 85% of the maximal rate. The maximal rate can be estimated from the formula (220 minus age) mentioned or, when available, directly obtained from the results of exercise testing. Thus, a 40-year-old person with a maximum heart rate of about 180 beats per minute would have a target training pulse rate between 136 and 153 beats per minute.

The training heart rate for patients with coronary heart disease and angina pectoris should be either 50% to 70% of Vo_2 max of their anginal threshold or 70% to 85% of the heart rate response that precipitates chest pain or ischemic ECG changes. Similarly, patients

who did not achieve their predicted maximum heart rate due to the development of other symptoms should train at 70% to 85% of their maximal attained heart rate. If a patient cannot exercise at this level, a reduced intensity for a longer duration should be encouraged, as endurance conditioning can occur even with lower training levels. Patients should be instructed on self-monitoring of their pulse rate with exercise and, with practice, will develop a sense of their exercise intensity that can guide subsequent training.

Each exercise session should begin with a 3- to 15-minute warm-up phase, which includes stretching of the muscles and tendons to be used during the activity. It is followed by a training period of 15 minutes to an hour and a cool-down phase, which usually consists of continued exercise at a reduced intensity to prevent postexercise hypotension. Exercise should be avoided soon after consuming alcohol or a heavy meal and during hot, humid and very cold weather. Proper dress for environmental conditions is mandatory.

The frequency of exercise should be a minimum of three training sessions that are equally spaced throughout the week. Although greater improvement in endurance conditioning results by increasing the duration and frequency of the exercise sessions, the risk of physical injury increases as well.

The first several weeks of training should be at a lower level of exertion—that is, 50% to 60% of the maximum heart rate—to allow for the development of motor skills and musculoskeletal conditioning. Following this, the duration, frequency and intensity of exercise can be gradually increased at two-week intervals, remembering that cardiovascular conditioning occurs best at exercise intensities that achieve a level of 70% to 85% of the maximum heart rate response. The intensity of exertion during training should never be prescribed beyond the level at which a patient has been tested.

Occupational demands or physical rehabilitation often require a specific training regimen; resistance exercises such as weight training are an example. Weight training can be beneficial for persons whose job involves lifting or pulling or for persons requiring specific musculoskeletal therapy. This isometric (static) activity helps develop greater strength but usually results in little or no endurance conditioning. Although strict isometric exertion has been only cautiously prescribed for patients who have cardiovascular disease, there is little objective evidence that this form of exercise is more hazardous than endurance activities. Because exercise ECG testing is generally restricted to endurance activities, however, patients with abnormalities identified during standard testing should limit training to endurance exercise. If isometric exercise is to be used, static testing with blood pressure and ECG monitoring should be done. Initially, weight training intensity should result in low levels of muscular tension. Slow progression toward higher resistance levels can be encouraged as strength increases.

Patients considered at high risk for complications during physical training should be followed in medically supervised programs in which close instruction, identification of contraindications and immediate treatment are available. Although infrequent, cardiac complications during exercise do occur. These include cardiac arrest, myocardial infarction and arrhythmias. Noncardiac complications, which are the most common cause of dropout from exercise programs, usually involve musculoskeletal injury. The most common include tendinitis, fractures and soft tissue injury.

Monitoring Training

Many cardiovascular adaptations are evident during the initial six weeks of training. Indicators of a conditioning effect include a decrease in resting pulse, a reduction in perceived exertion at previous intensities of exercise and the ability to handle greater workloads at the target heart rate. Documenting reductions in body fat, resting blood pressure and lipoprotein levels can be used as encouragement to continue exercising.

The use of the target heart rate and level of perceived exertion as a guide to training has been discussed. A useful intensity index of aerobic training is the ability to carry on a conversation during exercise. Inability to do this often indicates that the patient is training too vigorously and is beyond his or her anaerobic threshold.

Signs of overexertion can be manifest immediately or appear at a later time. Those that indicate immediate overexertion include inappropriate postexertional tachycardia (beyond ten minutes), angina, claudication, light-headedness, confusion, nausea, vomiting or uncontrolled dyspnea. More subtle indicators of overexertion that are delayed in onset are symptoms of prolonged fatigue, insomnia, or extreme muscle soreness often caused by rhabdomyolysis.

To maintain the benefits of exercise, physical activity must be continued on a regular basis. Fitness levels decrease to pretraining levels after several weeks of inactivity. Several weeks of exercise are needed for a patient to become accustomed to and enjoy a training regimen. Physician encouragement and frequent reinforcement of the projected long-term benefits of exercise are necessary during acclimatization to the exercise program. Structuring an exercise program to each person's needs, along with education and continued support, are usually required for success. Group participation is often useful in gaining patient acceptance and adherence to an exercise prescription.

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Withholding or Withdrawing Extraordinary Life Support

Optimizing Rights and Limiting Liability

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For many years physicians, ethicists and members of the legal community have attempted to minimize ambiguity and unpredictability in making decisions to withhold or withdraw extraordinary life support. Recent developments in national and California law now afford medical care providers unparalleled protection from criminal and civil liability in surrogate decision-making situations. They also reinforce the concept of patient's rights by providing medical care consumers with new and effective mechanisms for enforcing their "right to decide," even after they have lost decision-making capacity. A case in point is California's new Durable Power of Attorney for Health Care, which serves as a model for other jurisdictions that do not have such legislation. Thus, the medical and legal professions, working together, can contribute immeasurably to respectful medical decision making by educating the public about these developments and by adopting policies that reinforce these rights.

(Gilfix M, Raffin TA: Withholding or withdrawing extraordinary life support—Optimizing rights and limiting liability [Critical Issues in Medicine]. West J Med 1984 Sep; 141:387-394)

Until very recently, physicians, ethicists and members of the legal community were frustrated in efforts to minimize ambiguity and unpredictability in surrogate health care decision making for adults.* Short of court authorization by way of conservatorship, terminal care decisions were typically made by family members in consultation with the attending physician. This process was undermined and rendered unreliable by a lack of clear legal standards and rare but highly visible instances in which physicians have been sued or charged with criminal law violations (in some cases, both) for implementing decisions that were either made or sanctioned by family members.

Notwithstanding these problems, there is no question that withholding or withdrawing extraordinary life support is a common daily event in medical practice.[1-3] As are sound clinical judgment and working closely with patients and families, legislation and judicial support are critical to protecting patients' rights and limiting physician liability.[4] There are numerous subpopulations of patients wherein withholding or withdrawing extraordinary life support comes into play on a regular basis. For example, patients with malignant hematologic conditions who are admitted to intensive care units for severe medical problems have an overall mortality of 80% to 90%. In fact, in a recent study no patient with a hematologic cancer who was on a ventilator for more than five days survived to leave the hospital.[5] During the past year data were reported concerning the outcome of patients suffering cardiopulmonary arrests while in hospital.[6] Their overall survival was 14% at discharge and only 10% of these patients were alive six months later. In this investigation it was shown that patients who are intubated during cardiopulmonary resuscitation (CPR) have a 91% mortality and if CPR was given for longer than 15 minutes, the

*Because of the focus of this article, we will not discuss surrogate decision making for adults for whom no one has or will come forward.

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ABBREVIATIONS USED IN TEXT

CPR = cardiopulmonary resuscitation
DPAHC = Durable Power of Attorney for Health Care

mortality was 95%. Only one patient out of 52 who were in coma after 24 hours in hospital was able to be discharged, but this patient died two months later. Therefore, it is quite apparent that decisions to withhold or withdraw extraordinary life support need to be confronted on a regular basis and guidance is needed from a legislative and judicial standpoint.

New California legislation that became effective on January 1, 1984, is a step in this direction. It allows competent adults to appoint a surrogate decision maker for use in future health care decisions, when an adult might be unable to express his or her opinions. This represents a dramatic step forward in this inherently difficult and highly emotional area of law and medicine. It also provides long overdue protections to health care providers who must implement these decisions. It is hoped that it will serve as a model to the rest of the country.

In this article we discuss several legal vehicles that are available in the state of California to support patients' rights and limit physician liability when withholding or withdrawing extraordinary life support. For states without comparable legislation, we will explore the strengths and weaknesses of the "living will," the Natural Death Act of California that became effective on January 1, 1977, and, most important, the new Durable Power of Attorney for Health Care.

We will discuss the historical development of legal precedents and the development of the legal vehicles, or documents, identified above.

In-depth attention will be given to (1) the use and implications of the Durable Power of Attorney for Health Care in California, (2) physician liability and how it is affected by this new legislation and (3) practical recommendations for integrating this important new legal vehicle into the everyday practice of medicine.

Historical Development of Legal Precedents

No discussion of these issues is complete without a review of the Karen Ann Quinlan case,[7] even though the decision in that case has no legality outside the state of New Jersey. Indeed, no other case has captured the attention and the hearts of as many people. Its poignancy was accentuated when, after the New Jersey Supreme Court authorized removal of this attractive young woman's life-support system, she continued—and continues—to live with only nutrition and hydration assistance. In March 1984 Quinlan became 30 years old. She has been comatose for nine years.

Karen Ann Quinlan went into an incurable "chronic persistent vegetative state" for reasons that remain unclear. A return to any degree of sentient consciousness was deemed impossible. Expert opinion was that she would not survive without a respirator. Her father, Joseph Quinlan, petitioned to become her guardian for the express purpose of ordering withdrawal of the respirator. In granting Mr Quinlan's petition, the court found that Karen had a "right of privacy" that could be asserted by her guardian. Before the respirator was to be withdrawn, concurrence from the family, responsible attending physicians and the hospital ethics committee was to be obtained. Only in this way were the guardian, the physicians or other participants to be assured protection from criminal and civil liability.

The *Quinlan* case has had far more impact on public opinion than on subsequent court cases. Its precedent importance in California, for example, is minimal in light of case law development and legislation that will be discussed elsewhere in this article.

Shortly after the *Quinlan* decision in New Jersey, the Massachusetts Supreme Judicial Court addressed closely related issues in the *Saikewicz* case.[8] Mr Saikewicz, aged 67, was severely mentally retarded and terminally ill with leukemia. He was incapable of giving informed consent or refusing chemotherapy. The court was of the view that "extraordinary" medical means need not be used when there is no real hope of recovery. In a departure from *Quinlan,* it specifically indicated that court involvement in such cases is required. It then approved appointment of a guardian who was authorized to refuse chemotherapy treatments on behalf of Mr Saikewicz.

Equally noteworthy was *In the matter of Dinnerstein,*[9] which was also decided in the state of Massachusetts. It is significant because it did not involve decision making by the individual patient or by a court-appointed surrogate. It addressed a situation in which an incompetent patient was terminally and hopelessly ill. In such cases, the court held, the attending physician may order that no resuscitative efforts be made in the event of respiratory or cardiac arrest when the family concurs with the decision.

Another leading case in this area is a New York one, *Eichner v Dillon,*[10] which was decided by that state's highest court. Also known as the *Brother Fox* case, it confirmed adult patients' right to accept or reject medical treatment. Brother Fox, who was comatose and put on a mechanical respirator, had explicitly expressed his antipathy to such treatment in discussions he had had about the *Quinlan* case. Because the record established by clear and convincing evidence that he would have refused consent for the use of the respirator, the court ruled that its use must be discontinued. The key factor in the *Brother Fox* case was that he had unambiguously expressed his desires while competent. Because that court only specified the burden-of-proof standard—clear and convincing evidence—without limiting the way in which the standard must be met, both oral and written statements, such as those made in documents known as living wills, have importance and relevance in that jurisdiction.

The state of New Jersey is again contributing to the development of this area of law with the *Conroy* case—now on appeal to the New Jersey Supreme Court—which will have great impact on this area of the law.

A lower court ruled in *Conroy* that a nursing home resident of questionable decision-making capacity could not be allowed to die by the removal of a nasogastric tube through which nutrition and hydration were administered. Her family petitioned the court for approval, arguing that it was what she would have wanted. The court did not view Mrs Conroy as being in a vegetative state, thus distinguishing it from the *Quinlan* case.

Recent California Developments

Superior Court versus Drs Barber and Nejdl: Protection From Criminal Prosecution

Notwithstanding and perhaps because of these cases, many members of the legal and medical communities are of the view that the courts should have no role in so personal a decision-making process. Any debate on the subject is largely academic, however, because the existence of litigation cannot be denied. So serious is the problem that the mere filing of suit in any court of the country at any point in time—and notwithstanding the result of such litigation—has too often had a retarding and chilling effect on good judgment. Open discussion and common sense fall costly victims to this fear of controversy and litigation.

The fear is not always unjustified, as illustrated in a recent case involving two California physicians. Doctors Barber and Nejdl performed surgical closure of an ileostomy on Mr Clarence Herbert in a Los Angeles Kaiser Hospital. Mr Herbert unexpectedly suffered cardiopulmonary arrest shortly after that operation, went into a coma and was placed on a respirator.

After five days, the physicians determined that Mr Herbert's condition was irreversible and so advised his wife and family. With Mrs Herbert's consent, use of the respirator was discontinued. Mr Herbert continued to live without assistance from the respirator. Likely mindful of Karen Ann Quinlan, the physicians discussed withdrawing intravenous tubes through which nutrition and hydration were administered. Written spousal permission was obtained and administration of nutrition and hydration was terminated. Mr Herbert died six days later.

Doctors Barber and Nejdl were surprised, as was the entire medical community, when murder charges were subsequently filed against them by the Los Angeles District Attorney. A legal roller coaster followed, with a municipal court judge dismissing the murder charges, a superior court judge reinstating them and a court of appeals ultimately resolving the matter by effectively dismissing the charges in a precedent-setting opinion.

In that opinion, *Barber v Superior Court,*[11] the appellate court scolded the California legislature for failing to take the initiative. It stressed the lack of reliable standards and decision-making methods that would eliminate the need for court involvement. Such standards would, presumably, acknowledge the propriety of decision making first by the patient or, in cases of patient incapacity, by family members who would carry out the patient's wishes or act in the patient's best interest. The *Barber* court took a major and protective step forward in finding murder charges to be inappropriate. Going further, it outlined decision-making criteria that placed substantial reliance on the March 1983 report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research,[12] in identifying decision-making criteria in cases where life-sustaining procedures may be of questionable value. After confirming that a patient's wishes are always dominant, it addressed situations with a focus on whether a particular procedure was "heroic" or "extraordinary" and described a balancing analysis. That analysis focused on "whether the proposed treatment is proportionate or disproportionate in terms of the benefits to be gained versus the burdens caused."[13] The court went on:

> Under this approach, proportionate treatment is that which, in view of the patient, has at least a reasonable chance of providing benefits to the patient, which benefits outweigh the burdens attendant to the treatment. Thus, even if a proposed course of treatment might be extremely painful or intrusive, it would still be proportionate treatment if the prognosis was for complete cure or significant improvement in the patient's condition. On the other hand, a treatment course which is only minimally painful or intrusive may nonetheless be considered disproportionate to the potential benefits if the prognosis is virtually hopeless for any significant improvement in condition.[13]

Citing *Quinlan* and *Dinnerstein,* a very definite dichotomy was drawn by the court between a normal, sentient existence on the one hand and a "biological vegetative existence" on the other. Using this analysis, and because Mr Herbert was diagnosed as irretrievably comatose, the court then addressed the question of who should make treatment decisions. It noted that the physicians acted properly in relying on Mr Herbert's wife, who was identified as the most appropriate surrogate. In fact, Mrs Herbert was joined by eight of their children in deciding to withdraw the medical treatment. This decision was bolstered by reports that Mr Herbert told his wife that he did not want to "become another Karen Ann Quinlan."

The court of appeals held that the physicians' omission to continue treatment in the extant circumstances was not "an unlawful failure to perform a legal duty."

While *Barber* was decided at the district court level and is only binding precedent in the second district, it is the only case to address these issues and develop decision-making criteria or standards in the state of California. For this reason, California physicians operating within its boundaries are likely to enjoy substantial insulation from the criminal legal system. Less solace is found in the fact that both Drs Barber and Nejdl are currently being sued for civil damages by Mr Herbert's widow, despite her earlier participation in the decision making.

As will be discussed below, Drs Barber and Nejdl would have enjoyed a great deal of protection from a civil suit had a properly executed and legally reliable Durable Power of Attorney for Health Care in California been the basis of decision making.

Legal Documents Affecting Medical Care Decisions in California (Pre-1984)

What then can consumers do to enhance the likelihood that their wishes will be respected in the medical care context if they become incapacitated? Can any available approach afford physicians a reasonable degree of protection from criminal or civil liability in implementing decisions made by or for a comatose or otherwise incapacitated patient?

In endeavoring to answer these questions, three documents available to medical care consumers in California will be examined. The purpose is to identify the document or combination of documents that will afford consumers and practitioners alike the greatest possible degree of support. Also, these documents can serve as models for other states.

Legal Effectiveness of the Living Will

The "living will" is a document that, in one form or another, expresses a person's wishes that extraordinary medical procedures not be used if that person is terminally and hopelessly ill. The dominant form is distributed by Concern for Dying, a nationally known organization based in New York City. The living will remains a document of dubious legal reliability. While Concern for Dying argues cogently that it is legally enforceable, court review is sketchy and results are inconsistent at best.[14]

In Florida, for example, the first state appellate court to review the issue held that a living will is *not* a legal basis for terminating artificial life support systems (*Matter of Francis Landy,* Fourth District Court of Appeals, State of Florida, decided May 25, 1983, now on appeal to the Florida Supreme Court). It said that court approval of such an action is necessary in order for consenting family members, attending physicians and hospitals and their administrators to be relieved of civil and criminal liability. Significantly, the state of Florida has no legislation authorizing the use of living wills. There are no other reported cases in which the legal effectiveness of a living will, without basis in state legislation, has been examined.

It must be concluded that the living will, standing alone, cannot be relied upon with full confidence. This is particularly the case in states like California, where applicable legislation is on the books.

The California Natural Death Act Directive

More important than the living will is the "directive" of the California Natural Death Act.[15,16] It is more important because it can, in some circumstances, be legally binding on the treating physician. The Act itself provides, in essence, that in certain circumstances "life-sustaining procedures" may be withheld or withdrawn if a person is terminally ill. A number of requirements must be satisfied to take advantage of this legislation.[17] Because an exhaustive discussion of them is beyond the scope of this article, only the most prominent—and problematic—requirements are delineated here. This is to show how rarely a Natural Death Act directive is a legally enforceable document.

- A person must be 18 years of age or older and be mentally competent to sign a directive.
- Two witnesses are required, neither of whom can be related to the person, have an interest in the estate or be a medical care provider. There are special witness requirements if the person resides in a nursing home.
- Revocation is extremely easy. Mental competency is not required for revocation.
- The directive must be signed at least 14 days after the declarant has been certified in writing by the attending and another physician as being terminally ill. "Terminally ill" in this legislation means that the person is facing an imminent death. While the term "imminent" is not defined, it is generally understood to mean about two weeks. This is the classic "Catch 22" factor that severely undercuts the Act's effectiveness—a person must be diagnosed as having two weeks to live, then live two weeks and be able to sign the directive as a competent adult!
- The directive must be entered into the declarant's medical file, ensuring that the attending physician is aware of its existence.

Significantly, a physician who terminates life-sustaining treatment because of a legally binding directive is protected from civil suit or criminal prosecution for such an act. Even if all of these requirements are satisfied, however, a physician can also ignore the directive and use seemingly prohibited life-sustaining procedures with full impunity from civil or criminal liability. At most, the offending physician may be found guilty of "unprofessional conduct" by the California Board of Medical Quality Assurance.

In summary, a directive signed in advance of a "certified" terminal illness is not legally enforceable. Even in those rare cases where all legal requirements have been satisfied, physicians retain ultimate authority and can ignore the directive with relative immunity.

The greatest benefit of the Natural Death Act directive lies in the fact that, unlike the living will, it is a form that bears the imprimatur of the California legislature. Signing a directive before a terminal condition exists is a way of being "on record" that a person does not want life-sustaining procedures used if he or she is afflicted with a terminal condition and if such procedures would only serve to delay death for a short period of time.

California's Durable Power of Attorney for Health Care

Effective January 1, 1984, new California legislation (introduced by State Senator Barry Keene, who also authored the California Natural Death Act)[18,19] creating the Durable Power of Attorney for Health Care (DPAHC) represents the most dramatic step forward in the area of patients' rights. It is no less dramatic for health care providers who are simultaneously afforded greater certainty of decision making and a sub-

stantial measure of protection from civil and criminal liability. Such protections can have special significance in cases of terminal illness when providers rely on the decision of the person named in the DPAHC.

This legislation provides for the signing of a Durable Power of Attorney for Health Care in which a competent adult names another person—the "attorney in fact"—to make virtually all medical care decisions for the adult if and when the person lacks the capacity to make her or his own medical care decisions.

This new legislation is a logical extension of the well-established principle that any competent adult has the right to refuse medical treatment.* It also eliminates cumbersome, costly and typically inappropriate intervention by the court system when difficult medical care decisions are to be made.

Effect of Signing a DPAHC

The signing of a DPAHC does not automatically convey decision-making authority. The authority is a contingent one, that contingency being the subsequent incapacity or inability of the person to understand his or her medical care options and to give informed consent. Unless this contingency occurs, the document has no legal effect whatsoever.

This fact is highly significant for physicians and health care institutions. So concerned was the legislature about possible misunderstanding or abuse of this power that the legislation requires either (1) the inclusion of specific warnings in the document itself or (2) an attorney certification that the attorney has advised the principal of all the rights and powers conveyed by the signing of the DPAHC. A summary of these warnings set forth below will give the reader a fundamental understanding of the powers conveyed in this document and any limitations on those powers. These warnings are explicitly set forth in the sample DPAHC form (Figure 1).

Unless otherwise stated in the DPAHC, conveyed is the authority to consent, refuse or withdraw consent "to any care, treatment, service or procedure to maintain, diagnose or treat a physical or mental condition." The principal, or person signing the document, can specify any types of treatment or placements that are not desired. This opportunity to personalize or tailor the DPAHC to a person's unique circumstances is extremely significant and will be illustrated in the discussion that follows.

Unless an attorney certifies that the person signing a DPAHC has been advised of virtually all implications of the document, the warnings alluded to above must be included in it. An understanding of these warnings is essential for all medical care providers.

Power to decide. Most important, the document gives the attorney-in-fact the power to make all health care decisions, including consent or denial or withdrawal of consent for any type of care or treatment. The principal may tailor the document to special needs or desires. For example, a 45-year-old woman who has Alzheimer's disease may direct that in no event may a respirator be used to maintain her life. She may identify medical care placements and treatments that she specifically rejects or welcomes.

It belabors the obvious to say that this allocation of authority is the most serious a person can make. In most cases, a patient will execute a general, unspecific DPAHC that conveys total decision-making power to the attorney-in-fact, perhaps specifying only that either minimum or maximum treatment be given in the event that there is no likelihood of recovery. In rare circumstances, an educated, sophisticated patient can prepare a future care plan, replete with lists of acceptable or unacceptable drugs, time limitations or selected therapies, including a description of circumstances when no resuscitative efforts are to be used.

Either approach has extraordinary and heretofore-unheard-of significance for treating physicians. Difficult issues include situations in which, for example, a duly empowered attorney-in-fact rejects treatment recommendations the physician believes the patient would accept if she or he retained capacity, situations in which specified care decisions were based on dubious information or misinformation and situations where the attorney-in-fact acts in a manner that is inconsonant with the terms of the DPAHC.

Before proceeding to an examination of duties under a DPAHC, it is important to know what powers an attorney-in-fact does *not* have. The designated person cannot, under any circumstances, consent to placement in a mental health treatment facility or to convulsive treatment, psychosurgery, sterilization or abortion.

Duties of attorney-in-fact. The attorney-in-fact has the duty to act consistently with the principal's desires. These desires can be expressed in the document itself or be made known to the attorney in any other way. In either case, the expressed desires of the principal must be followed. If the attorney-in-fact has no specific guidance from the principal, it is the attorney's duty to act in the principal's "best interest," a term inevitably undefined in the legislation.

The President's Commission considered the meaning of a "best interest" standard. It suggested adoption of the "reasonable person" approach, which would include assessment of "such factors as the relief of suffering, the preservation or restoration of functioning and the quality as well as the extent of life sustained." Such an assessment would also consider "the satisfaction of present desires, the opportunity for future satisfactions and the possibility of developing or regaining the capacity for self-determination."[12(pp135-136)]

Decisions resulting in death. Unless otherwise specified, the DPAHC includes the power to terminate or withhold treatment that is keeping the principal alive, where such termination or withholding is an otherwise legal act. A principal may, by the same token, specify that under no circumstances is he or she to be allowed

*See *Cobbs v Grant*,[20] which held that battery is committed when a physician performs treatment without an informed consent. See also *In the matter of Vincent M. Young*[21] where the court affirmed the power of a conservator to accept or refuse medical treatment, including a decision to terminate a conservatee's life-support systems.

to die when death is avoidable for any period of time, notwithstanding costs or possible side effects of necessary treatment.

This point bears emphasis because it underscores the neutrality of this legislation on the "right to die" versus the "right to live" controversy. The principal may, for example, want no or minimal medical intervention when that person is terminally ill. The principal would

DURABLE POWER OF ATTORNEY FOR HEALTH CARE

I [name of principal], of [city], County of [name of county], California, acting as principal, hereby declare this to be a durable power of attorney for health care under the provisions of Sections 2356, *et seq*, of the California Civil Code. I hereby appoint [name of attorney in fact] of [city], County of [name of county], California, to act as my attorney in fact to make health care decisions for me to the same extent as I could make such decisions if I had the capacity to do so. If [name of attorney in fact] is for any reason unwilling or unable to serve, I appoint [name of successor] of [city], County of [name of county], California, as my successor attorney in fact to make health care decisions.

WARNING TO PERSON EXECUTING THIS DOCUMENT

This is an important legal document. It creates a durable power of attorney for health care. Before executing this document, you should know these important facts:

1. This document gives the person you designate as your attorney in fact the power to make health care decisions for you, subject to any limitations or statement of your desires that you include in this document. The power to make health care decisions for you may include consent, refusal of consent, or withdrawal of consent to any care, treatment, service or procedure to maintain, diagnose or treat a physical or mental condition. You may state in this document any types of treatment or placements that you do not desire.

2. The person you designate in this document has a duty to act consistent with your desires as stated in this document or otherwise made known or, if your desires are unknown, to act in your best interests.

3. Except as you otherwise specify in this document, the power of the person you designate to make health care decisions for you may include the power to consent to your doctor not giving treatment or stopping treatment that would keep you alive.

4. Unless you specify a shorter period in this document, this power will exist for seven years from the date you execute this document and, if you are unable to make health care decisions for yourself at the time when this seven year period ends, this power will continue to exist until the time when you become able to make health care decisions for yourself.

5. Notwithstanding this document, you have the right to make medical and other health care decisions for yourself so long as you can give informed consent with respect to the particular decision. In addition, no treatment may be given to you over your objection, and health care necessary to keep you alive may not be stopped if you object.

6. You have the right to revoke the appointment of the person designated in this document by notifying that person of the revocation orally or in writing.

7. You have the right to revoke the authority granted to the person designated in this document to make health care decisions for you by notifying the treating physician, hospital or other health care providers orally or in writing.

8. The person designated in this document to make health care decisions for you has the right to examine your medical records and to consent to their disclosure unless you limit this right in this document.

9. If there is anything in this document that you do not understand, you should ask a lawyer to explain it to you.

I am executing this durable power of attorney for health care at _____ (city and state) on _____ (date).

_____
(name of principal)

State of California)
County of _____) ss.

On this _____ day of _____, in the year _____, before me, the undersigned, a Notary Public for California, personally appeared [name of principal], known to me (or proved to me on the oath of _____), to be the person whose name is subscribed to the within instrument and acknowledged to me that she or he executed the same.

I declare under penalty of perjury that the person whose name is subscribed to this instrument appears to be of sound mind and under no duress, fraud, or undue influence.

WITNESS my hand and official seal.

_____
Notary Public for California

My commission expires _____

As an alternative to notarization, a Durable Power of Attorney for Health Care may be witnessed by two witnesses, with certain restrictions applying. If the principal is a resident of a skilled nursing facility, one of the two witnesses must be a "patient advocate or ombudsman" designated by the California Department of Aging.

Figure 1.—Sample Durable Power of Attorney for Health Care (DPAHC) form.

explain this approach in the DPAHC and appoint a person who will, if necessary, take all lawful acts to effectuate these views.

Another person may want every conceivable medical intervention to prolong her or his life, notwithstanding prognosis or expected benefit. This would be explained in that person's DPAHC and he or she would appoint an appropriate person to carry out these wishes.

Effective duration of DPAHC. Unless the document specifies a shorter period, it is good for seven years. Necessarily, if the principal is unable to make medical care decisions at the end of the seven years or a shorter specified time period, it has ongoing validity until the principal regains such capacity.

Ongoing authority of principal. Notwithstanding the existence of a signed DPAHC, the principal retains full decision-making authority so long as that person is able to do so. The principal is also presumed to have capacity if he or she objects to any health care decisions made by the attorney-in-fact.

Revocation of DPAHC. Revocation can be achieved by either oral or written notification to the attorney-in-fact or the health provider. The responsibility to respect revocation, even if uttered by a patient with questionable capacity, is so necessarily grave that the failure to respect it can, in extreme cases, result in homicide charges being brought against the responsible person.

Rights regarding medical records. Unless otherwise specified in a DPAHC, the person designated has the right to examine the principal's medical records and to consent to their disclosure.

Protection From Liability

Section 2438(a) of the California Civil Code now specifies that the health care provider "is not subject to criminal prosecution, civil liability or professional disciplinary action . . . if the health care provider relies on a health care decision and both of the following requirements are satisfied":

1. The decision is made by an attorney-in-fact who the health care provider believes in good faith is authorized (under this legislation) to make the decisions.

2. The health care provider believes in good faith that the decision is not inconsistent with the desires of the principal as expressed in the durable power of attorney or otherwise made known to the health care provider, and, if the decision is to withhold or withdraw health care necessary to keep the principal alive, the health care provider has made a good faith effort to determine the desires of the principal to the extent that the principal is able to convey those desires to the health care provider and the results of the effort are made a part of the principal's medical records.

It is at once comforting to the physician and, yet, conceptually inconsistent to note an accompanying disclaimer in this same section of the civil code.[22] The disclaimer is so potentially broad that it is already raising serious questions in the legal and medical communities. It states that a physician is equally free to *reject* an attorney-in-fact's decision and refuse "to withdraw health care necessary to keep the principal alive" without fear of criminal prosecution, civil liability or professional disciplinary action.

The careful health care provider, then, is given a heretofore-unknown measure of protection in making and implementing decisions to utilize or forego life-sustaining procedures. Had Mr Herbert executed a Durable Power of Attorney for Health Care in which he named his spouse, it is likely that Doctors Barber and Nejdl would have been spared their ongoing involvement with the California system of justice.

Because the health care provider can be viewed as a primary beneficiary of California's new legislation, the reader is urged to pay special attention to policy recommendations that are set forth later in this article.

DPAHC Form

The legislation realistically acknowledges the fact that many Californians will want to use a form DPAHC. For this reason the legislation identifies warnings and other selected language that *must* be in a DPAHC. Nevertheless, the California legislature has as yet adopted no legislation that sets forth the most basic language of a model form.

As of this writing, legislation specifying the precise content of a basic DPAHC form has been introduced in the California legislature ([SB 1365] again by California State Senator Barry Keene), but it has not received formal attention. If adopted, the form will be effective as of January 1, 1985. It bears emphasizing that this legislation would create a model form only. Other, equally viable documents will be available from other sources and, in any event, the opportunity to draw up a DPAHC to fit an individual person's needs will always exist. Because the future of this proposed legislation is impossible to predict, and because an example of a DPAHC will be both educative and illustrative, one is shown as Figure 1.

Who Can Be Named Attorney-in-Fact?

Almost anyone can be designated attorney-in-fact so long as that person is a resident of the state of California. It is at once surprising and understandable that a person's immediate heir can be so named. Notwithstanding an arguable conflict of interest—a life-and-death decision for the principal may determine when and if the heir will inherit an estate—the immediate heir is typically the person most likely to understand the principal's attitudes and wishes in the event of a terminal or other serious medical condition.

The patient's medical care provider cannot be named, nor can the operator or any employee of a community care facility. The principal's conservator under the Lanterman-Petrie-Short (LPS) Act is also excluded unless the conservatee's attorney signs a special certification that is set forth in the statute.

Witnessing Requirement

A DPAHC can be witnessed in one of two ways. One is by a notary public, who must use the precise language set forth for notarization in this legislation. Such language goes beyond a notary's normal standard of care and includes a declaration that the principal "appears to be of sound mind and under no duress, fraud or undue influence."

The alternative is to obtain the signature of two witnesses, for whom specific declaratory language is also set forth. No one involved in the principal's health care or who operates or works for a community care facility can serve as a witness, nor can the attorney-in-fact. At least one witness must be unrelated and have no interest in the principal's estate.

Using language that is virtually identical to witness provisions for the California Natural Death Act directive, the Act requires residents of skilled nursing facilities to have a special witness. One such witness must be a "patient advocate or ombudsman as may be designated by the California State Department of Aging for this purpose." While no such "patient advocates" exist, the California Department of Aging does oversee a statewide network of long-term care advocates who can presumably serve as witnesses in such cases. Interested persons can contact the California Department of Aging offices of long-term care for referral to such programs in virtually every part of California.

Necessity of Institutional Policies

Health care providers and institutions have a very special responsibility and a very special opportunity. The responsibility is to become educated about these new medicolegal developments, to educate patients about them and, above all, to ensure that they make a difference.

The opportunity is to implement policies that respect patient needs and simultaneously take legitimate advantage of new protections in the law for health care providers.

More specifically, we recommend that health care providers take the following steps:

- Become educated and sophisticated about this area of medicine, ethics and law. Understand the use and effectiveness of the DPAHC and other related documents.

- Support efforts to educate the general public about new laws and how to take advantage of them. Foster the notion that good planning and "preventive law" is as important as preventive medicine.

- Develop unobtrusive and respectful methods for educating new patients and their families about DPAHCs, Natural Death Act directives and living wills. Make such documents available to interested persons. In so doing, great care must be taken to avoid even the appearance of duress or "undue influence."

- Ensure that patients and their families have access to independent sources of advice about medical care decision making. This could be done, in part, by developing a referral list of knowledgeable attorneys or other advisors.

- Establish mechanisms, such as ELM (ethical-legal-medical) committees, to create policies in these areas and to respond to new or problematic developments. Representatives of all three fields, as well as the community at large, should serve on such committees.

- Establish in-house mechanisms to be sure that all care providers know, for example, that a patient has executed a DPAHC and who the attorney-in-fact is. For example, orange dots may be placed on the files, charts and records of all patients who signed such documents. A computer code would be similarly utilized.

- Be sure comprehensible information about risks, benefits and implications of particular medical treatments is actually given to patients, their families and their surrogate decision-makers. The President's Commission also emphasizes the need for "procedures to enhance the patient's competence . . . [and] to overcome the influence of dominant institutional biases."[12(p4)] In this context, too, it is vital that both the appearance and the fact of "undue influence" by the physician or other provider be guarded against.

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Preoperative Evaluations by an Internist—Are They Worthwhile?

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The value of preoperative examinations done by internists on ophthalmology patients was assessed. A retrospective chart review of 258 consultations was conducted and information about surgical risk, as defined by strict criteria, was abstracted. A total of 59 surgical risk conditions and 62 incidental problems were detected. In 65% of the risk conditions internists intervened to lessen the patients' risk. Most of these benefits were in patients older than 60 years and very few important problems were detected in those younger than 50. The average cost of the consultation and additional laboratory tests was $146.60. It is concluded that significant benefit was derived at a reasonable cost by patients older than 50 years.

(Levinson W: Preoperative evaluations by an internist—Are they worthwhile? [Health Care Delivery]. West J Med 1984 Sep; 141:395-398)

With the rising costs of medical care, physicians must be increasingly critical of whether their services significantly benefit patients and at what cost. It seems most important to evaluate those services or tests that are frequently or routinely done. A service that general internists frequently perform is the preoperative evaluation of surgical risk. A consultation service was established in 1981 at the Good Samaritan Hospital and Medical Center, Portland, to provide preoperative evaluation of patients undergoing surgical procedures of the eye. This study was designed to determine if these evaluations actually helped detect and treat surgical risk factors, and the cost at which they were obtained.

Methods

All charts of patients seen by an internist before eye operations at the hospital between April and July of 1981 were reviewed retrospectively. Good Samaritan is a 539-bed community hospital with an accredited internal medicine residency program. Whether an internal medicine consultation was obtained was determined by the ophthalmologists. Most patients having operations did see an internist unless they were very young or had no medical problems. The consultations were done by a group of 11 general internists on a rotational basis.

The specific questions considered in the study are the following: Did the internists detect risk factors important to surgical outcome through history, physical examination and laboratory tests? Did the internists intervene to lessen surgical risk? Did they delay or cancel surgical procedures? Did they detect or treat postoperative problems? Were any problems unrelated to the operation discovered that required medical attention? Were any preventive health measures initiated by the internists?

A total of 258 cases were reviewed by a trained medical records abstractor. All notes and orders written by the internists were reviewed and the following information collected: surgical risk factors, therapeutic changes instituted, medical problems incidental to the surgical state, laboratory tests ordered, recommendation for type of anesthesia or for surgical delay, preventive health measures and postoperative complications. Standardized criteria were used to define surgical risk factors (described below). Results of all laboratory tests done were noted as either normal or abnormal as defined by laboratory normal ranges. Any abnormal results of laboratory tests ordered by the internists but not mentioned in the chart notes were flagged for the investigator's attention. In addition, all cases where a life-threatening event occurred were reviewed by the investigator to consider whether, in retrospect, some indication of a problem was overlooked by the internist. The investigator also reviewed all charts where a significant surgical risk factor was noted to ensure

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that the risk criteria were applied correctly. Demographic data were abstracted from all charts.

To define a surgical risk condition, strict criteria were established before data collection began. Only conditions documented in the recent medical literature to independently and significantly increase operative morbidity or mortality were included. Goldman identified a set of conditions correlated with the increased cardiac complications in noncardiac surgical procedures (Table 1).[1] These criteria were applied to assess cardiac risk factors. Notably excluded were hypertension (unless diastolic blood pressure was greater than 110 mm of mercury), bifascicular block, stable angina, mitral valve disease and congestive heart failure without a third heart sound or jugular venous distension.[2-4] Chronic lung disease was considered a surgical risk if the forced expiratory volume in one second (FEV_1) was less than 70%, midexpiratory flow rate was less than 200 liters per minute or if carbon dioxide partial pressure (P_{CO_2}) was greater than 45 or oxygen partial pressure (P_{O_2}) was less than 60 mm of mercury.[5-7] If pulmonary function tests or arterial blood gas determinations were not carried out, the investigator had to rely on the particular clinician's statement of severity of disease based on history or physical examination. If the clinician considered the patients to have severe lung disease, this was accepted as a surgical risk condition. Laboratory abnormalities including a serum potassium concentration of less than 3.0 mEq per liter, hematocrit less than 30% and serum creatinine greater than 3.0 mg per dl were considered risk factors.

TABLE 1.—*Cardiac Risk Factors*

Third heart sound or jugular venous distension (more than 12 cm above 4th intercostal space)
Myocardial infarction in preceding 6 months
Rhythm other than sinus or premature atrial contractions
More than five premature ventricular contractions per minute
Intraperitoneal or intrathoracic aortic operation
Age greater than 70 years
Significant aortic stenosis
Emergency surgical procedure
Poor general medical condition

TABLE 2.—*Age Distribution*

Age (Years)	*Number of Patients N=258*	*Patients With Surgical Risk Condition*	
		Number	*(Percent)*
<20	7	0	(0)
20-29	6	1	(17)
30-39	5	1	(20)
40-49	12	0	(0)
50-59	21	4	(19)
60-69	81	15	(19)
>70	126	30	(24)

TABLE 3.—*Surgical Risk Conditions*

Surgical Risk Condition	*Number of Times Noted*	*Therapeutic Change*
Aortic stenosis	3	0
Atrial fibrillation	6	2
Premature ventricular contractions, more than 5 per minute	1	1
Congestive heart failure	3	1
Recent acute myocardial infarction	1	1
Paroxysmal atrial tachycardia	1	0
Previous postoperative pulmonary embolus	1	1
Recent syncope (unknown cause)	2	0
Recent transient ischemic attack	1	0
Myasthenia gravis	1	1
Uncontrolled seizures	1	1
Hypokalemia (<3.0 mEq/liter)	6	6
Hypoglycemia	1	1
Anemia (hematocrit, <30%)	1	1
Asthma, severe	4	4
Chronic lung disease, severe	22	16
Ethanol withdrawal	2	1
Adrenal insufficiency	1	1
Hypothyroidism	1	0
TOTAL	59	39

In all conditions that were potential risk factors for which no criteria had been established a priori, the investigator made a determination of risk based on recently published reviews.[4,6] All such cases are presented in the results section. It is worth mentioning several conditions that were not considered independent surgical risk factors since they occurred frequently. Diabetes mellitus was not considered a risk factor unless ketoacidosis was present at the time of operation. Goldman's data indicated that diabetes was not an independent risk factor for cardiac complications of surgical procedures.[1] The risk of sepsis that may be increased during general surgical procedures for diabetes is not a significant problem in eye operations.[4] The presence of asymptomatic carotid bruits and the history of remote transient ischemic attacks were similarly not included.[8]

The cost of each consultation was calculated including the average physician fee and the average cost of laboratory tests generated by the internist's orders. The cost of medication ordered and investigation that may have resulted from the discovery of incidental findings after admission to hospital were not included. Routine laboratory tests included blood urea nitrogen, potassium, serum glutamic oxaloacetic transaminase and glucose determinations, hemogram and analysis of urine. Two of the ophthalmologists included an electrocardiogram and x-ray study of the chest in their routine preoperative orders in patients older than 40 years, while the other ophthalmologists ordered them as required.

Results

A total of 258 charts were reviewed. There were 151 female and 107 male patients. Most were older than 60, 31% were between 60 and 69 and 49% were 70 years of age or older. The exact age distribution is shown in Table 2.

There were 59 conditions considered important to surgical risk noted in 51 patients (Table 3). If the in-

TABLE 4.—*Incidental Findings*

Findings	*Number of Cases*
Carotid bruit	15
Congestive heart failure (no third heart sound or jugular venous distension)	5
Cardiomegaly	1
Uncontrolled hypertension	17
Mitral regurgitation	8
Aortic stenosis	13
Chronic alcohol abuse	1
Diabetes, uncontrolled	2
Newly diagnosed diabetes	3
Enlarged thyroid	7
Multinodular goiter	1
Symptoms suggestive of hypothyroidism	2
Hypokalemia (serum potassium, 3 to 3.5 mEq/liter)	6
Cerebellar ataxia	1
Depression	1
Steroid myopathy	1
Syncope	2
Dementia	1
Gingivitis	1
Hepatomegaly	3
Leukoplakia	1
Rectal bleeding	4
Benign prostatic hypertrophy	6
Hematuria	2
Urinary tract infection	2
Chronic obstructive lung disease, mild or moderate	7
Anemia	5

ternist ordered a medication or other therapeutic maneuver to improve a condition, it is indicated as a "therapeutic change" in the second column of Table 3. In 38 of the 59 conditions a therapeutic change was made. A therapeutic intervention was not always available. For example, in the three cases of significant aortic stenosis, patients had increased surgical risk but there was no specific intervention available to decrease that risk. Most therapeutic changes were adjustments in anticoagulants, diuretics, potassium supplements or bronchodilators.

All the surgical risk conditions were detected in patients older than 50 except for one patient with a history of postoperative pulmonary embolus and one with asthma. Four patients with significant problems were between 50 and 59, 15 were between 60 and 69 and 30 were 70 years of age or older (Table 2).

In all, 62 problems incidental to surgical condition but possibly important to a patient's general well-being were detected (Table 4). Included were three patients with previously unrecognized diabetes mellitus. Again, these incidental findings were mainly in patients older than 50. In patients younger than 50 the incidental findings included uncontrolled diabetes (one patient), uncontrolled hypertension (one), enlarged thyroid (one), newly noted anemia (one) and mitral valve murmurs of uncertain significance (three).

The preventive health measures included 151 breast examinations, 11 pelvic examinations, 125 rectal examinations and 3 immunizations. In addition, specific mention was made of smoking advice in 13 consultations and assorted preventive health maneuvers were documented in 8 other cases.

Operations were delayed in four cases. One patient with atrial fibrillation and a rapid ventricular rate received digoxin and the surgical procedure was done later the same day. In another patient with ischemic changes on an electrocardiogram there was a delay of several hours to obtain a past electrocardiogram for comparison. Two other patients had operations delayed for one and two days, respectively, due to a potassium level of 2.8 mEq per liter and a significant anemia requiring transfusion.

Postoperative problems were noted in eight patients: congestive heart failure (one patient), digoxin toxicity (one), rapid atrial fibrillation (one), urinary tract infection (one), frequent premature atrial contractions (one), urinary retention (one) and increasing angina (two). In three of these patients surgical risk conditions had been found preoperatively. The patient with urinary retention had a potassium level of 2.7 mEq per liter, which was corrected before operation. One patient with angina had atrial fibrillation and significant aortic stenosis. The patient with rapid atrial fibrillation was noted to have the same rhythm preoperatively but with a slower rate.

The three life-threatening perioperative complications included a third-degree heart block requiring placement of a pacemaker, a cerebrovascular accident one day postoperatively and an intraoperative bradycardia requiring interruption of the operation. In this case no serious cardiac problems were detected and the bradycardia was considered due to a bulbovagal response. In reviewing the three charts, the investigator did not find anything in the preoperative consultation or laboratory test that gave a warning of possible complications.

All 313 abnormal laboratory tests not mentioned in the consultation were reviewed. Of these, most were considered minor abnormalities compared with normal laboratory values. For example, analysis of urine might have shown one to two leukocytes per high-power field. In 11 cases the abnormalities were considered clinically significant by the investigator. In one case, thyroid function studies showed pronounced abnormalities and, in another, 3+ glycosuria and an elevated blood glucose level were noted in a patient not known to have diabetes. In nine patients, pulmonary function tests were ordered and no comment was made about significant abnormal results.

The total cost of the routine preoperative laboratory tests was $52.10. For those patients requiring an electrocardiogram and an x-ray study of the chest routinely, the cost was $132.10. In 92 of the 258 cases, no further tests were ordered by the internists. Internists ordered one test each in 72 patients, two tests in 70 patients, three tests in 16 patients and more than three tests in 8 patients. The average cost of preoperative testing beyond the routine panel was $40.30. Most often that cost was incurred by an x-ray film of the chest, electrocardiogram, electrolyte study or arterial

blood gas determination. Postoperatively a total of 51 tests was ordered with an average cost to the patient of $25.

The average cost of the internist consultation was $95. If an additional visit was made, an additional $22 charge was incurred. Of the patients, 28% had at least one follow-up visit.

Including the consultation fee and laboratory tests, the average cost was $146.60.

Discussion

There is a great deal of legitimate concern about the cost of medical care, particularly with respect to "routine" health examinations. Insurance companies are reevaluating whether they should pay for routine preoperative consultations by internists. Although this study is not able to compare the outcome for patients who have preoperative internist care with the outcome for those who do not, one can still consider whether the consultations have offered anything to operative candidates.

Surgical risk factors were found in 51 of the 258 patients, and the internists provided therapeutic measures to decrease that risk in approximately two-thirds of those. Severe chronic obstructive lung disease was the surgical risk condition most frequently noted. This was probably due to the less objective definition of this condition compared with other surgical risk factors. Only two surgical conditions of the 59 detected (3.4%) were in patients younger than 50 years despite the fact that 11% of patients were in that age group. This suggests that routine consultation in patients younger than 50 is not valuable in finding surgical risk conditions unless a history suggests important potential problems. On the other hand, in the patients older than 50 years an important surgical risk condition was detected in approximately 20%. Routine consultation in this group seems warranted.

In addition, 62 problems incidental to surgical procedures but potentially important to a patient's health were found. Some of these may have previously been detected by the patients' physicians but some were important unappreciated problems (the three cases of newly diagnosed diabetes, for example). As was found with the surgical risk conditions, most incidental findings were in patients older than 50 years. How many of these problems received adequate follow-up is unknown. Only a few postoperative problems were detected by the internists and none of these were of an urgent or emergency nature.

Routine health care did receive attention by the internists but this may not be the most appropriate setting for these evaluations or procedures. Often these internists had no continuing relationship with the patients and were not aware of the patients' previous routine care from other physicians.

This study shows that internists detect and treat an important number of surgical risk conditions during preoperative evaluations of patients scheduled to have eye operations. In patients younger than 50, benefits were derived infrequently and consultations should only be obtained in limited circumstances in this age group. Because an uncomplicated cataract operation costs $3,500 to $4,000 including surgeon's fees and hospital costs, an internist's evaluation for $146.60 represents only a small fraction of the total bill. In my opinion, this relatively small increase in cost seems worthwhile in light of the benefits derived.

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Medical Schools of the West

The University of Colorado School of Medicine

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On May 5, 1883, the Board of Regents of the University of Colorado directed the first president of the university, Joseph Addison Sewell, MD, to establish a medical school in Boulder. The primary reason for this action was to increase the enrollment of the university. Four months later, on September 5, the school was opened with a faculty of four members, two students and a two-year curriculum. The budget of the school at that time was $2,600 or about 10% of the appropriation from the General Assembly of Colorado to run the university. In 1892 the curriculum was expanded to four years.

In 1909 Abraham Flexner visited Colorado and reviewed the schools of medicine in the state. In the ensuing monumental report, he urged the university to amalgamate its medical education effort with the private medical school in Denver (itself a combination of two earlier schools, Denver and Gross). This was made possible by a 1910 amendment to the Colorado State Constitution, which allowed moving the clinical years to Denver and also made it possible for the union to occur. In 1924 a 17-acre campus was established in South Denver on which were constructed a medical school, a nursing school, the Colorado General Hospital and the Colorado Psychopathic Hospital. This campus "out in the prairie" has served as the home for the University of Colorado School of Medicine since that date.

In its first 100 years, the University of Colorado School of Medicine (UCSM) has had 19 deans including Maurice H. Rees, who served for 20 years (1925 to 1945). Today, the school is one of the five major units on the Health Sciences Center campus (Figure 1), which includes the School of Nursing, the School of Dentistry, Colorado General Hospital and Colorado Psychiatric Hospital. The deans of the schools and directors of the hospitals report to a chancellor, who in turn reports to a president. The president is responsible for the four campuses of the University of Colorado system, each of which has a chancellor. The ultimate governing body is an elected nine-member Board of Regents, which was established when the Colorado constitution was adopted in 1876.

Undergraduate Medical Education

The entering class at UCSM numbers 125 and the student body size reaches 525. The attrition rate varies between 1% and 2% per class and in excess of 95% of those admitted are Colorado residents (468 of the student body in 1982). The proportion of state residents in recent years has been steadily increasing. For the fall 1982 entering class, 197 women applied; of these, 38% (51) were admitted. Of the class, 11% (13 students) are members of minority races according to the criteria established by the Board of Regents.

The undergraduate curriculum of the UCSM is traditional in format with a disciplinary orientation. Recently a number of interdisciplinary courses have been started including one in neurosciences, one concerned with an introduction to clinical medicine and one in pathophysiology. Over the past ten years, the school has also conducted an experimental anatomy course in which students could either study anatomy involving dissection of the cadaver in the traditional way or they could take the course through the sole use of prosections. Outcomes from the anatomy experiment have indicated that students learn slightly better with the nondissection approach.

Students are required to take the usual clerkships including medicine (12 weeks), pediatrics (6 weeks), psychiatry (6 weeks), surgery (12 weeks), obstetrics and gynecology (6 weeks), neurology (2 weeks) and primary care (6 weeks). A considerable amount of time is available in the fourth year for electives including study abroad and rotations in a statewide Area Health Education Program called SEARCH.

Two major problems confront undergraduate medical education at UCSM. The first involves the class size

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Figure 1.—The University of Colorado School of Medicine is one of five major units on the Health Sciences Center campus, which includes the School of Nursing, the School of Dentistry, Colorado General Hospital and Colorado Psychiatric Hospital.

and raises the question, Should the University of Colorado School of Medicine, given the apparent overproduction of physicians in the country, reduce the number of students admitted? The answer to this question has been negative primarily because Coloradoans already have significantly less access to medical education than the national average. In addition, the population of Colorado is steadily growing and is expected to reach 4 million by 1990, or 1 million more than the 1980 census.

The second problem relates to the tuition charged at UCSM. In the 1960s, the General Assembly of Colorado decided that it was not unreasonable to ask every Colorado resident who received an education in the state to pay 25% of the costs. This has resulted in an in-state tuition for entering medical students at UCSM of $5,986 for the 1982-1983 academic year. In 1981-1982, the tuition level in Colorado was the highest among the state-supported US medical schools and in 1982-1983, UCSM ranked second. A number of states, including New Jersey, Vermont, Wisconsin and New York, however, have increased tuition over the past year and are now approaching the levels charged at the UCSM. The national average for in-state tuition at state-supported institutions for the 1982-1983 academic year was $2,686 and the national mean was $2,675. In contrast to resident tuition rates, all nonresidents at UCSM are required to pay $26,337, the highest in the country.

While there will be a number of effects of high tuition rates, three seem most ominous. First, a number of persons will fail to consider medicine as a career option because of the high costs. As such, schools of medicine with inordinately high fees could very likely become schools for the very poor or the affluent. Second, some students will have to decline offers of admission because they cannot afford to attend. Third, some students will fail to complete their studies in the usual time and some may drop out permanently because of financial exigency. None of these options are congruent with the concept of equal access to medical education for all segments of our society.

Graduate Medical Education

At present the University of Colorado trains 663 house-staff officers including clinical fellows in all disciplines of medicine. The operation of this enterprise is accomplished through a single integrated graduate medical education program with a budget of about $12.5 million. The program offerings represent the affiliated residency programs in 19 different institutions. This integration has made it possible to establish a self-insured malpractice trust for the residents as well as a medical, dental and disability program that has been functioning smoothly and effectively for the past few years. This mechanism not only reduces the premium necessary for malpractice, but provides more control of events that lead to malpractice suits.

The problems at the graduate medical education level are the following: First, how many house staff should be trained in each discipline? Second, where can the financial support be obtained to offer competitive house-staff stipends? Third, what is the purpose of house-staff training—education or service? Fourth, how should the malpractice situation—especially involving affiliated hospitals and "residents of the University of Colorado School of Medicine"—affect UCSM's affiliation agreements?

Continuing Medical Education

Colorado has become a very popular place to visit and vacation. From UCSM's viewpoint, an undesirable component of this fact is that many universities and organizations use the Colorado mountains for continuing education purposes. This, coupled with a growing number of private agencies in Colorado that are offering continuing medical education courses, makes the continuing medical education market very competitive. Until recently the state of Colorado required continuing medical education for physician licensure and the local demand increased the number of enrollees in UCSM-sponsored courses. However, with the recession and a possible removal of the requirement for licensure, the number of enrollees has decreased.

Specifically, during the 1981-1982 academic year, the University of Colorado School of Medicine offered 24 continuing medical education courses. The 1,997 people who attended came from 39 states and nine foreign countries. An associate dean is the responsible administrator and a faculty advisory committee is appointed each year to review courses, advise on policies and directions, look for new markets and establish general policy. The cost of operating the courses is removed from the total income and the remaining "profits" are distributed to those departments involved in the profit-making courses. About 10% of the profits are used for academic enrichment for the school at large. Hence, the distribution of these funds provides an incentive for faculty and departments to participate in the programs.

Allied Health Programs

The University of Colorado School of Medicine offers three allied health programs. These include physical therapy (which is the only such program in the state and admits about 30 students per year), medical technology (the first such program in the United States and admits 20 students) and the Child Health Associate Program (known as CHAP and the first of its kind in the United States). The Child Health Associate Program has served as a model for nurse practitioner programs elsewhere and currently admits 44 students per year.

TABLE 1.—*University of Colorado School of Medicine Grants and Contracts*

Calendar Year	*Total Million*	*Federal Million*	*Non-Federal Million*
1977	$25.1	$21.3	$3.8
1978	27.6	23.3	4.7
1979	32.1	27.5	4.5
1980	34.3	28.4	5.9
1981	31.3	22.8	8.5
1982	33.3	26.7	6.5

In addition to the allied health programs, the medical school faculty participate in a variety of master's and PhD degree graduate programs. These are administered by a graduate school coordinator on the Health Sciences Center campus who in turn reports to the president of the university. Master's degrees are offered in six disciplines and PhD degrees in nine disciplines. In addition to formal graduate education, the school offers a variety of one- to three-year postdoctoral training programs that attract persons from all over the world.

Research

In general, biomedical research has played a prominent role in the overall growth and development of the University of Colorado School of Medicine. Total grants and contracts have grown from $25.1 million to $34 million per year during the past five years (Table 1). Of this, federal sources have grown from $21.3 to $24.4 million and nonfederal sources have grown from $3.8 to $8.5 million. At present 38.6% of faculty salaries depend on grants and contracts and, hence, this activity has become an integral part of the School of Medicine.

Cancer biology, neurosciences, immunology, cell biology and developmental and molecular biology are areas of special emphasis today. Among the major contributions of the past has been the Denver Child Development Scale, which is used around the world. In addition, the Denver Classification of Human Chromosomes is widely accepted and the pioneering application of ultrasound scanning to diagnostic medicine first occurred in Colorado. The child abuse syndrome was defined in Denver, the world's first liver transplant was carried out at the School of Medicine and the world's first perinatal medicine division was also established at the University of Colorado.

A number of challenges face the research activities of the school. These include the evolving university-industry relationships, the uncertainty of federal grants and contracts, the difficulty in meeting space and equip-

ment needs of faculty and especially the younger faculty, the limited number of physicians choosing full-time careers in research and the difficulty of obtaining graduate student and fellowship stipends.

Patient Care

The university owns and operates a 400-bed hospital known as the University Hospital-Colorado General. This hospital, which derived from the old Colorado General Hospital, was statutorily established primarily for the care of medically indigent persons, or those who could not provide for themselves. This statutory requirement for the care of indigents has created continuous and ongoing financial distress for the institution. This distress is compounded by a history of extensive "line-iteming" and poor funding by the Colorado legislature. Beginning with the 1982 fiscal year, however, the legislature granted budget flexibility to the University of Colorado for the operation of its University Hospital. This, in essence, allowed the hospital to carry forward into the next fiscal year any unspent revenues in the form of reserves, depreciation allowances, capital purchases and the like. In addition, Robert Dickler, the hospital administrator, has initiated major changes. The hospital has never been in better fiscal condition. Morale and optimism have never been higher.

While most of the emphasis has always focused on Colorado General Hospital, the university operates a second hospital by state statute. This is the University Hospital-Colorado Psychiatric Hospital. Administratively separate with its own budget, the Colorado Psychiatric Hospital operates 35 inpatient beds and an extensive outpatient service, and represents the primary acute care hospital in the state. The Chairman of the Department of Psychiatry is by state statute the superintendent of the hospital and has responsibility for the hospital's budget and personnel. This hospital has been effectively managed over the years and consistently has had positive fiscal balances at year end.

The two hospitals, together with the major affiliated hospitals of Denver General Hospital, The Childrens Hospital, The National Jewish Hospital and Asthma Research Center, Rose Medical Center and Denver Veterans Administration Medical Center, have a total of some 1,800 beds that are used for education and research purposes. Of these, the Denver VA Medical Center is the most closely linked to the university; it is now undergoing a $60 million renovation and expansion program.

Turning to professional fees, a state statute mandated that before July 1, 1981, all professional fees earned by the faculty of the School of Medicine had to be used solely for faculty salaries. In addition the state's legislature looked upon this Faculty Practice Fund cash as a revenue source and, therefore, felt comfortable in appropriating a portion of the cash to support education or other state activities. This resulted in a series of operating deficits in the school's Faculty Practice Fund (Table 2) and repeated financial crises. This chaotic financial situation was compounded by the statutory

TABLE 2.—*Fiscal Summary of UCSM Faculty Practice Fund*

FY	Patient Cash Million	Excess (Deficit) Million	Debt Million
1975-1976 ..	$ 4.95	($0.8)	($1.36)
1976-1977 ..	6.30	(1.04)	(2.40)
1977-1978 ..	6.7	(0.45)	(2.86)
1978-1979 ..	6.9	(1.44)	(4.30)
1979-1980 ..	8.4	1.06	(4.20)
1980-1981 ..	9.5	1.09	(4.10)
1981-1982 ..	12.7	2.90	(3.70)
1982-1983 ..	15.3	3.70	(3.05)

TABLE 3.—*UCSM Faculty Practice Fund—Professional Fees Related to Medically Indigent Patients*

Year	Amount	Reimbursement Million
1982-1983	$.....	$1.25
1981-1982	9,425,804	1.00
1980-1981	7,244,875	0.75
1979-1980	4,200,424	0.00
1978-1979	4,815,810	0.00
1977-1978	4,783,174	0.00
1976-1977	4,858,482	0.00
1975-1976	3,042,323	0.00
1974-1975	2,929,244	0.00
1973-1974	2,478,454	0.00
1972-1973	2,266,548	0.00
1971-1972	2,487,156	0.00

mandate to provide medically indigent care at Colorado General and Colorado Psychiatric Hospitals.

Beginning in 1979-1980, things began to change. In that year, the finances of UCSM reversed the previous pattern and the new trend has continued to the present. In 1980-1981, the legislature began to appropriate funds for the faculty's efforts in providing care for the medically indigent. This has increased slightly in each subsequent year but still represents only a small percentage of the total care provided (Table 3).

In addition, in 1981 the Colorado General Assembly unanimously approved the establishment of a nonprofit foundation outside of the University of Colorado for billing and collecting professional fees. In July 1982 this Colorado Medical Services Foundation was activated following final approval by the Board of Regents. The foundation provides an incentive, not only for the school and departments, but also for each faculty member, who can increase his or her salary by a factor of 50% by seeing patients. As a result of this program, the cash generated from the practice of medicine has doubled since 1978-1979.

In the patient care area, a number of significant problems remain. These include a heavy medically indigent responsibility with inadequate reimbursement for physician effort, the uncertainty of medicare-medicaid regulations reimbursement and an oppressive state personnel and purchasing system. The latter is especially vexing for a school of medicine such as the UCSM with its multitudinous sources of revenues, each of which has special regulations.

TABLE 4.—*UCSM Faculty Salary Sources, 1982-1983*

Source	*Amount Million*	*Percentage*
State	$ 9.3	27.6
Grants and contracts	13.0	38.6
Colorado Medical Services Foundation	11.4	33.8
TOTAL	$33.7	100.0

Faculty

For the 1982-1983 academic year, the University of Colorado School of Medicine had 604 full-time faculty members on the main campus. In addition, there were 229 full-time faculty members at affiliated institutions, including the VA Medical Center, The Childrens Hospital, Denver General Hospital and the National Jewish Hospital/Asthma Research Center. The efforts of the 833 full-time faculty are supplemented by 2,193 voluntary faculty. The faculty salaries are derived from three sources (Table 4) and provide some protection against variations in the salary sources.

Among the challenges in the faculty area, the most annoying is the tenure issue. If state-supported full-time equivalents are used as a tenurable base, then UCSM was significantly overtenured over the past ten years. With the establishment of Colorado Medical Services Foundation and resignations, this matter has nearly reversed itself to a balance between tenured faculty and full-time equivalents. It does not allow, however, for the tenuring of junior faculty, which is very discouraging to young academicians.

The second problem relates to salaries. At the basic science level, salaries are generally competitive in the range of the Association of American Medical Colleges' 50th percentile figures. On a clinical science level, at the lower ranks, salaries are also reasonable. At the higher clinical ranks, however, the salaries have been embarrassingly low. The 29.9% increase in salaries and bonuses that has been paid since fiscal year 1980-1981 (two years) has helped but the issue remains.

Budget

The School of Medicine's 1982-1983 budget was $81.7 million. This was derived from state sources (17.7%), grants and contracts (42%), patient care (19.9%) and tuition, graduate medical education, continuing medical education, gifts and bequests (20.4%).

In the past, budget inflexibility, which was mandated by the state's legislature, was compounded by the inflexible state personnel and state purchasing system. Beginning in July 1982 the Health Sciences Center campus received budget flexibility similar to that which had been obtained earlier for the University Hospital. With some minor program exceptions, including family medicine and physician reimbursement for the care of medically indigent, this flexibility has provided many new options for the financial management of UCSM. One specific outcome had been the ability to maximize the use of the limited dollars available. However, in spite of the budget flexibility, the school has had only limited state support and, in fact, has received less state funds than most state-supported medical schools in the West. This limited support has led to an increasingly greater dependency on grants and contracts, which in turn was enhanced by limited clinical income.

Future

There are many reasons to be optimistic about the future growth and development both in size and quality of the University of Colorado School of Medicine. Among them is the emergence of Denver as a business, communication, transportation and banking center. In addition, Colorado has impressive energy resources including shale oil, coal and uranium. In the past five years, Colorado has undergone a major building boom, which corresponds to an increase in the population. It is expected that the state's population will reach 4 million by 1990, 1 million more than at present, and that most of this growth will occur in Denver.

As noted, there have also been a number of changes at the legislative level, which has been very encouraging. And the potential exists for an expanded tax base in Colorado. These factors, together with the quality of the faculty, the leadership of the university, the abundant clinical resources without severe competition in the practicing community and the attractive surroundings, make the future of the University of Colorado School of Medicine most encouraging.

Public Health and Preventive Medicine

Chronic Obstructive Lung Disease

PETER RANK, JD, *and* DILEEP G. BAL, MD, MPH, *Sacramento, California*

One of a series of articles from western state public health departments

From 1979 to 1980, the two most recent years for which there are data, the percentage increase in the chronic obstructive lung disease (COLD) mortality clearly surpassed that of every other leading chronic cause of death. COLD, also known as chronic obstructive pulmonary disease (COPD), now ranks as the fifth leading cause of death in California and is recognized, along with other smoking-related diseases such as lung cancer and coronary heart disease, as a major cause of preventable death.[1]

While data between 1950 and 1980 are not strictly comparable, mortality from COLD during that 30-year period rose from 8.8 per 100,000 (0.9% of all deaths) to 25.8 per 100,000 (3.3%). Death rates from this growing group of diseases doubled between 1950 and 1960 and the mortality rate from a single disease—emphysema—increased a dramatic fourfold during the same period.[2] Moreover, in 1960 COLD appeared among the ten leading causes of death for the first time, ranking ninth and causing 1.9% of all deaths. During the last two decades, mortality from COLD has continued to increase but at a slower rate. More recently, the percentage changes in the number and rate of COLD deaths increased 14.7% and 12.7%, respectively, from 1979 to 1980.[3] These changes were surpassed only by influenza and homicide and by no chronic conditions. Over the past decade death rates from COLD were highest among whites and males, although the relative rate of increase over time was greater for women—a phenomenon thought to be attributable to the smoking behavior of women.[4]

In order to define those diseases qualifying as COLD, the American Lung Association and the California State Department of Health Services convened a panel of pulmonary experts chaired by Kenneth Moser, MD, of the University of California, San Diego. The approach selected was to categorize all possible COLD subdiagnoses from *International Classification of Diseases* (ICDA) Eighth and Ninth revisions (ICDA-8, ICDA-9) and adopt that terminology upon which a consensus was reached. Codes accepted for use under ICDA-9 fell under a rubric entitled "chronic obstructive pulmonary diseases and allied conditions" (ICDA-9 Codes 490-496). Although not strictly comparable, disease entities accepted under ICDA-8 were unqualified bronchitis, chronic bronchitis, emphysema, asthma, chronic interstitial pneumonia, bronchiectasis and COLD without mention of asthma, bronchitis and emphysema (ICDA-8 Codes 490-493, 517, 518, 519.3).[5,6]

Under ICDA-8, changes in the certification of COLD deaths (specifically an increased use of ICDA-8 code 519.3—COLD without mention of asthma, bronchitis and emphysema—instead of more specific COLD entities) resulted in an apparent decrease in COLD mortality. During the 1970s, deaths from asthma, chronic and unqualified bronchitis and emphysema all appeared to be decreasing. During 1971, the initial year of its utilization, code 519.3 was assigned to 675 deaths, or 15.4% of all COLD deaths. By 1978 this percentage had risen to nearly 50% of all COLD mortality, or 2,853 deaths. The increase in mortality due to code 519.3 more than compensated for the decline in rates from asthma, bronchitis and emphysema combined.

Since these mortality statistics reflect only underlying causes of death certified as being due to COLD, cause-specific mortality rates seriously underrepresent true COLD mortality. Data extracted from multiple cause of death tapes supplied by the National Center for Health Statistics indicate, for example, that for every death certified as due to emphysema in 1978, there were nearly two others where emphysema was listed as an "other" condition present at the time of death (California Department of Health Services, Center for Health Statistics, unpublished data).

Other researchers have shown that COLD has been underreported on death certificates, and the true mortality rate from this disease is probably underestimated by vital statistics death rates.[7]

In spite of the problems encountered in preparing a

(Rank P, Bal DG: Chronic obstructive lung disease [Public Health and Preventive Medicine]. West J Med 1984 Sep; 141:404-405)

Dr Rank is Director of the California Department of Health Services, and Dr Bal is Chief of the Adult Health Section, California Department of Health Services, Sacramento.

Reprint requests of Dileep G. Bal, MD, MPH, Chief, Adult Health Section, California Dept of Health Services, 714 P Street, Room 499, Sacramento, CA 95814.

ABBREVIATIONS USED IN TEXT

COLD = chronic obstructive lung disease
ICDA-8, ICDA-9 = *International Classification of Diseases,* Eighth and Ninth revisions

definitive study of COLD in California, it was clear that COLD, although underreported on death certificates, is a major and growing public health problem. As such, it deserves our careful and thoughtful attention to its identification, causes, treatment and prevention.

Mortality from other leading causes of California deaths—such as cardiovascular disease, cerebrovascular disease and accidents—has decreased in the period during which rates from COLD have shown dramatic increases. This should alert the medical community to the increasing importance of COLD as a leading cause of death.[8]

Studies have shown that cigarette smoking is the leading contributor to the development of bronchitis and emphysema.[9] These facts, in combination with the staggering economic and health costs related to two other major smoking-related diseases—lung cancer and heart disease—should continue to alert health professionals to the growing need for developing statistical reporting systems to improve disease definition and surveillance, and for research to determine feasible interventions to delay, mitigate or prevent COLD.[10] Equal time and energy must be devoted to promoting effective strategies to prevent the onset and increase of those diseases with known behavioral or causative factors.

As health professionals committed to disease prevention and health care cost containment, we must aggressively pursue all the opportunities and resources available to encourage and educate the public to adopt healthy, nonsmoking life-styles.

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In Memoriam

California Medical Association

ALLEGRINI, ANTHONY F., Santa Cruz. Died April 6, 1984, in Santa Cruz, aged 75. Graduate of Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1934. Dr Allegrini was a retired member of the Santa Cruz County Medical Society.

BATTAGLIA, SALVATORE D., San Jose. Died May 4, 1984, in Palo Alto of heart disease, aged 66. Graduate of St Louis University School of Medicine, 1945. Licensed in California in 1945. Dr Battaglia was a member of the Santa Clara County Medical Society.

FINK, LESLIE A., San Francisco. Died May 12, 1984, in San Francisco of myocardial infarct, aged 57. Graduate of Medical College of Georgia, Augusta, 1954. Licensed in California in 1958. Dr Fink was a member of the San Francisco Medical Society.

FRENCH, LINDOL R., San Francisco. Died May 7, 1984, in Sunnyvale, aged 78. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1932. Licensed in California in 1936. Dr French was a retired member of the San Francisco Medical Society.

HART, HELEN B., Santa Barbara. Died March 28, 1984, aged 74. Graduate of the University of Rochester School of Medicine and Dentistry, 1935. Licensed in California in 1937. Dr Hart was a retired member of the Medical Society of Santa Barbara County.

MURPHY, WILLIAM R., Sacramento. Died April 11, 1984, in Sacramento of malignant lymphoma, aged 71. Graduate of the Creighton University School of Medicine, Omaha, 1940. Licensed in California in 1940. Dr Murphy was a retired member of the Sacramento-El Dorado Medical Society.

NESS, ANSTEN R., Los Gatos. Died April 24, 1984, in Los Gatos, aged 71. Graduate of Tulane University School of Medicine, New Orleans, 1940. Licensed in California in 1944. Dr Ness was a retired member of the Santa Clara County Medical Society.

OHANNESON, FRANK, Sacramento. Died March 13, 1984, in Oceanside of leukemia, aged 92. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1918. Licensed in California in 1919. Dr Ohanneson was a retired member of the Sacramento-El Dorado Medical Society.

PACE, PAUL T., San Jose. Died May 15, 1984, in Thousand Oaks, aged 81. Graduate of Tulane University School of Medicine, New Orleans, 1926. Licensed in California in 1927. Dr Pace was a retired member of the Santa Clara County Medical Society.

SANCHEZ, A. ERNEST, San Diego. Died April 4, 1984, in San Diego of amyotrophic lateral sclerosis, aged 59. Graduate of the University of Chicago School of Medicine, 1957. Licensed in California in 1958. Dr Sanchez was a member of the San Diego County Medical Society.

SCHULTZ, HERBERT H., San Francisco. Died October 13, 1983, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1925. Licensed in California in 1925. Dr Schultz was a retired member of the San Francisco Medical Society.

SLEATH, JACK C., Nipomo. Died October 2, 1983, aged 76. Graduate of Yale University School of Medicine, New Haven, 1935. Licensed in California in 1937. Dr Sleath was a retired member of the Medical Society of Santa Barbara County.

STURGES, KEITH W., Arcata. Died April 13, 1984, in Arcata of injuries received in a light airplane accident, aged 51. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1959. Licensed in California in 1961. Dr Sturges was a member of the Humboldt-Del Norte Medical Society.

TRIFON, HARRY M., Palo Alto. Died November 9, 1983, aged 76. Graduate of Tulane University School of Medicine, New Orleans, 1933. Licensed in California in 1954. Dr Trifon was a retired member of the Santa Clara County Medical Society.

Utah State Medical Association

CORNWALL, CHARLES RALPH, Salt Lake City. Died May 12, 1984, in Salt Lake City, aged 89. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1924. Licensed in Utah in 1925. Dr Cornwall was a member of the Salt Lake County Medical Society.

QUINN, JAMES HENRY, Salt Lake City. Died May 7, 1984, in Salt Lake City, aged 67. Graduate of Washington University School of Medicine, St Louis, 1943. Licensed in Utah in 1949. Dr Quinn was a member of the Salt Lake County Medical Society.

SKIDMORE, EARL L., Salt Lake City. Died May 22, 1984, in Salt Lake City, aged 94. Graduate of Columbia University College of Physicians and Surgeons, New York, 1918. Licensed in Utah in 1919. Dr Skidmore was a member of the Salt Lake County Medical Society.

Washington State Medical Association

ARONSON, SAMUEL F., Bellevue. Died January 8, 1984, in Seattle, aged 74. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in Washington in 1937. Dr Aronson was a retired member of the King County Medical Society.

BARNES, MARTIN S., Burlington. Died March 26, 1984, in Burlington, aged 71. Graduate of the University of Rochester School of Medicine and Dentistry, 1943. Licensed in Washington in 1962. Dr Barnes was a retired member of the Skagit County Medical Society.

MOORE, GEORGE B., Suquamish. Died March 29, 1984, aged 77. Graduate of the University of Arkansas School of Medicine, Little Rock 1930. Licensed in Washington in 1933. Dr Moore was a retired member of the King County Medical Society.

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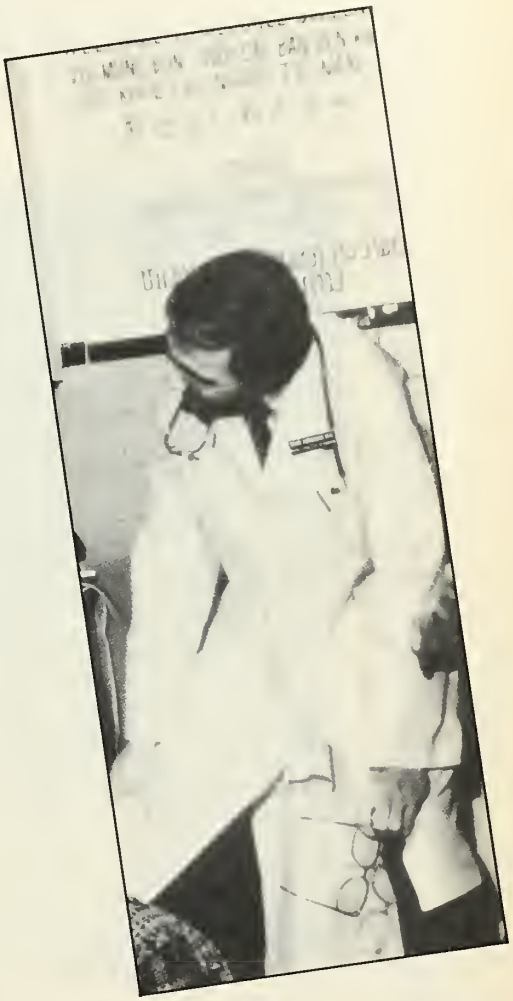

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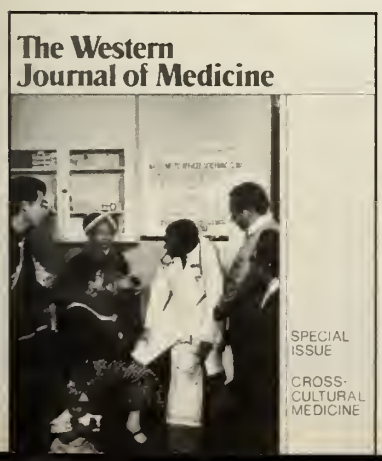

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B

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CONTINUING MEDICAL EDUCATION

(Continued from Page 319)

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October 2-6—**1st Annual Endurance Sports Medicine Symposium.** American Medical Joggers Association at King Kamehameha Hotel, Kona, Hawaii. Tuesday-Saturday. Contact: Ferdy Massimino, Dept. of Emergency Medicine, 2312 Haverhill Dr., Benicia 94510. (707) 745-2954.

November 9-11—**Sports Medicine and Outpatient Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Friday-Sunday. Contact: Jackie Shiller, CMEA. PO Box 84296, San Diego 92138. (619) 223-2997.

SURGERY

September 16-20—**American Academy of Otolaryngology Annual Meeting** at Las Vegas. Sunday-Thursday. Contact: L. Douglas Cox, Dir. Meetings/Expeditions, 1101 Vermont Ave., NW, Ste. 302, Washington, DC 20005. (202) 289-4607.

September 17-21—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

September 20-22—**Microsurgery: An Introduction to Microtechnique for Small Artery and Nerve Repair.** American Academy of Orthopaedic Surgeons at San Diego. Thursday-Saturday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

October 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

October 1-5—**Second Annual Vascular Surgery Board Certification Review.** UCLA at Miramar Sheraton Hotel, Santa Monica. Monday-Friday.

October 6-13—**6th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott. Hawaii. One week.

October 9-14—**American Society of Plastic and Reconstructive Surgeons Inc., American Society of Maxillofacial Surgeons Inc. and Plastic Surgery Educational Foundation Meeting** at Las Vegas. Tuesday-Sunday. Contact: ASPRS-PSEF, Exec. Office, 233 N. Michigan Ave., Ste. 1900, Chicago 60601.

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October 10-14—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. 34 hrs. $1,200.

October 11-13—**Controversies in Urology.** American Urological Association at San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, PO Box 25147, Houston, TX 77265. (713) 799-6070.

October 14-18—**Western Orthopedic Association Meeting** at San Diego. Sunday-Thursday. Contact: WOA, 1970 Broadway, Ste. 1235, Oakland 94612. (415) 893-1257.

October 14-18—**Preparing for Surgery: Medical Evaluation of the Preoperative Patient.** UCD at Doubletree Inn, Monterey. Sunday-Thursday.

October 17-21—**Advanced Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. $1,200.

October 21-26—**American College of Surgeons Meeting** at San Francisco. Sunday-Friday. Contact: ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 24—**Spinal Update 1984.** UCSF at Hyatt Regency Hotel, San Francisco. Wednesday. 18 hrs. $295. Contact: UCSF (415) 666-5731.

October 26-29—**Total Knee and Hip Arthroplasty "Hands On" Course.** Center for Health Education, Long Beach. Friday-Monday. 20 hrs. Contact: Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 27—**Lumbar Spine and Pelvis.** UCSD at Hotel del Coronado, Coronado. Saturday.

October 28-November 9—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 29-November 3—**Basic Microsurgery Training Workshop.** UCSD at Surgery Research Lab, University Hospital, San Diego. Monday-Friday. $1,200.

November 9-10—**American Academy of Facial Plastic & Reconstructive Surgery: Soft Tissue Workshops.** The San Francisco Head and Neck Surgery Foundation at Holiday Inn Union Square, San Francisco. Friday-Saturday. Contact: Cynthia Ashe, SFHNSF, 350 Parnassus Ave., Suite 502, San Francisco 94117. (415) 221-8487.

November 12-16—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday,

November 28-December 2—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday.

November 30-December 2—**Bone Grafting for Maxillofacial Indications.** Plastic Surgery Research Foundation at Hotel Intercontinental, San Diego. Friday-Sunday. $295.

December 1-8—**Temporal Bone Surgical Dissection—1984.** House Ear Institute at Los Angeles. 62 hrs. One week. Contact: Antonio de la Cruz, MD, Director of Education, HEI, 256 South Lake Street, Los Angeles 90057. (213) 483-4431.

December 3-5—**Current Trends in Total Knee Arthroplasty.** American Academy of Orthopaedic Surgeons at Lake Tahoe. Monday-Wednesday. Contact: AAOS, 444 N. Michigan Avenue, Chicago, IL 60611.

December 3-7—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs.

December 6-9—**The Adult Hip.** American Academy of Orthopaedic Surgeons at Rancho Mirage. Thursday-Sunday. Contact: AAOS, 444 N. Michigan Avenue, Chicago, IL 60611.

December 12—**Orthopedic Surgery-Arthroscopy—Diagnosis and Treatment.** LLU. Wednesday.

December 14—**A Modern Look at Trauma.** Daniel Freeman Memorial Hospital, Inglewood. Friday. 6 hrs. Contact: DFMH, Dept. of Medical Education, (213) 674-7050, Ext. 3427.

OF INTEREST TO ALL PHYSICIANS

September 17-19—**Relational Issues of Addiction: Violence, Sexuality and Intimacy.** Scripps Memorial Hospital at Vacation Village Hotel, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, Conf. Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

September 17-21—**Office Procedures.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Friday.

September 19-21—**State of the Art in the Care of Geriatric Patients: Pre-Intra-Post-Operative Management.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $325. Contact: Robin B. Jackson, Office of Cont. Ed., PO Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

September 19-23—**Annual Scientific Program and Postgraduate Course of the Pacific Coast Fertility Society** at Marriott's Rancho Las Palmas, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

September 20-23—**34th Annual Obesity and Associated Conditions Symposium.** American Society of Bariatric Physicians at MGM Grand Hotel, Reno. Thursday-Sunday. 17 hrs. Contact: Randall B. Lee, Exec. Dir., 4730 E. Caley Ave., Ste. 210, Englewood, CO 80111. (303) 779-4833.

September 21—**Dermatology and Dermatologic Office Procedure Workshop.** CME at Kona Kai Club, San Diego. Friday. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 23—**Dermatology and Dermatologic Office Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Sunday. $175. Contact: J. Shiller, Continuing Medical Education Associates, PO Box 84296, San Diego 92138. (619) 223-2997.

September 28-30—**Stress and Coping: A Weekend Workshop for Lesbian Physicians.** CMA at Stanford Sierra Lodge, South Lake Tahoe. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

September 29—**Food Allergy: Update 1984.** Los Angeles Society of Allergy and Clinical Immunology at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Geri Coldewey, LASACI, 1626 North Wilcox, #557, Hollywood 90028.

October 1—**Nutrition Symposium.** UCSF at Yosemite. Monday.

October 3-7—**Ways to Wellness.** LLU at Americana Canyon Hotel, Palm Springs. Wednesday-Sunday. 10 hrs.

October 7-9—**The Neural and Metabolic Bases of Feeding.** UCD at Napa Valley Holiday Inn, Napa. Sunday-Tuesday.

October 8-19—**Intensive Residency in Occupational Medicine.** UCSF. 2 weeks. 65.5 hrs. $1,000.

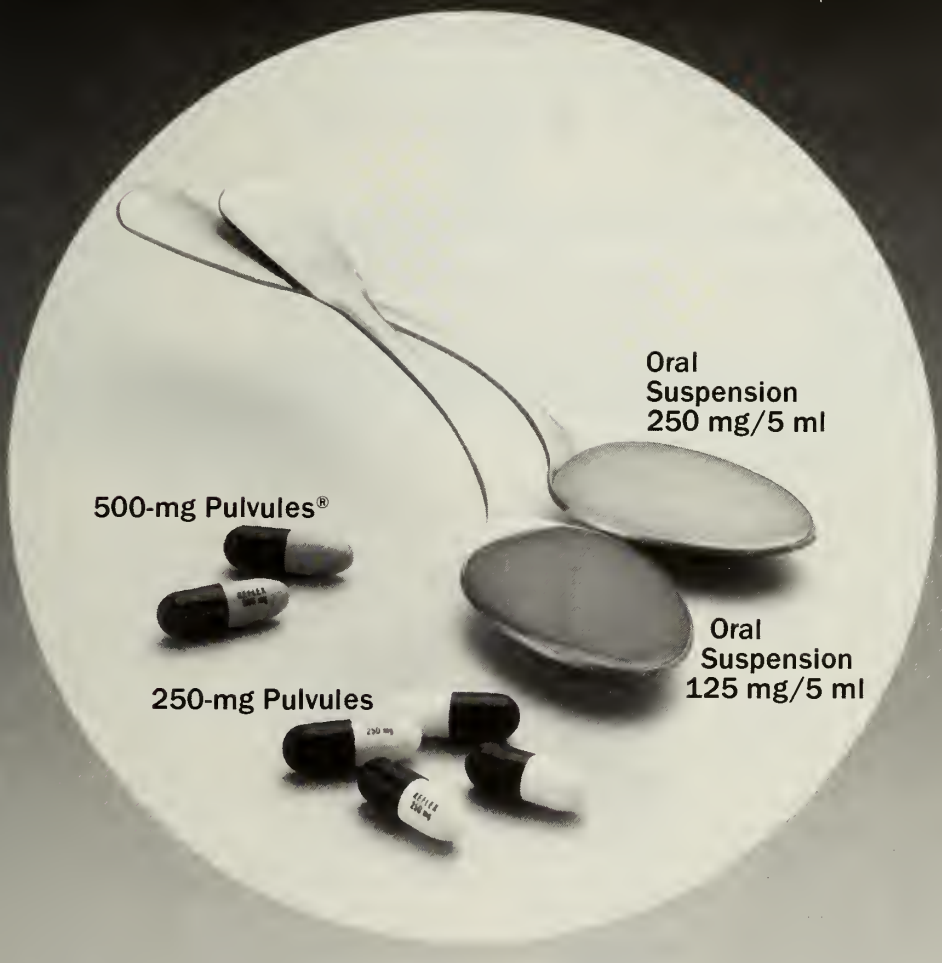
October 11-14—**A California Conference in Applied Clinical Geriatrics.** UCD at Napa Valley. Thursday-Sunday.

October 12-13—**Skin From A to Z.** UCSF. Friday-Saturday.

October 12-13—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $200.

(Continued on Page 424)

Easy To Take



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PHYSICIANS WANTED

GENERAL INTERNIST, Board certified/eligible: Multi-specialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact A. J. Grose, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

INTERNIST, Board certified or eligible, to join Monterey County, California, 5-physician group, all Board certified. Competence in Intensive Care necessary. Send curriculum vitae to Box 6412, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

BOARD CERTIFIED Oncologist, Cardiologist, Internist, Neurosurgeon, Otorhinolaryngologist for Southeastern Washington—Tri-Cities, 150,000 population. Outdoor activities abound. Group or solo opportunities. Contact Vesta Skiens, Kennewick General Hospital; (509) 586-6111 (309).

GENERAL SURGEON, SUN VALLEY, IDAHO. Energetic general surgeon to practice with multi-specialty group. Well equipped adjacent hospital. Quality of life high, income moderate. Curriculum vitae and references with first letter please. Dr Lynn T. Levy, PO Box 66, Sun Valley, ID 83353.

FAMILY PRACTITIONER, BC/BE for challenging work with Community Clinic. 3 days per week plus call, OB included. Benefits. Send CV to Betty Arterberry, Personnel Officer, Sonoma County Indian Health Project, Inc., 2240 Professional Drive, Santa Rosa, CA 95401.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436 or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

WANTED: Family practitioners who are Board certified or Board eligible and/or have at least two years of related clinical experience. Will provide ambulatory services in a primary care program consisting of a central primary care center and six satellite clinics. The clinical facilities include laboratory, x-ray and pharmacy support services to allow for a comprehensive range of diagnostic and treatment capabilities. Responsibilities will include the clinical supervision of family nurse practitioners, sharing of on-call assignments, in addition to providing ambulatory medical care to a general population. The salary and fringe benefits are competitive. This program is under the direction of the Sacramento County Health Department. For further information, contact Dr Peter Kho, Medical Director, Clinic Services Branch, Sacramento County Health Department, 3701 Branch Center Road, Sacramento, CA 95827, or call (916) 732-3687.

CALIFORNIA—Growing family practice group needs Board Certified FP with OB skills in Mountainous Resort Area—Send inquiries to Randall Meredith, MD, P.O. Box 1880, Weaverville, CA 96093.

PHYSICIANS WANTED

GENERAL SURGEON TIRED OF CONGESTION AND SMOG?—Board certified or Board eligible. To join eight member Family Practice medical center. Have full-time radiologist. Major specialties consult on regular basis. Located at International Falls in northern Minnesota. Near Voyageurs National Park. Year around outdoor recreation abounds. Served by major airline. Population twenty thousand. Send curriculum vitae to Dr James R. Schuft, Falls Medical Center, Shorewood Dr, International Falls, MI 56649.

ALASKA—Opportunities for board certified or eligible Family Practitioner, Pediatrician, and Orthopedic Surgeon in multi-specialty 20-physician group in Fairbanks. An opportunity to practice quality medicine in a unique setting in the heart of Alaska's interior with outstanding outdoor recreational opportunities. Fairbanks is a community of 30,000 with a trading population of 65,000. Clinic located two miles from modern 183-bed community hospital and four miles from the cultural center, University of Alaska campus. Excellent compensation and benefit package. No immediate investment. Excellent growth potential for energetic individual. First year salary guarantee with incentive. Send curriculum vitae to Ron Davis, Manager, Tanana Valley Clinic, 1001 Noble Street, Fairbanks, AL 99701.

GENERAL SURGEON, Board certified/eligible: multispecialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership anticipated. Contact J. W. Devney, MD, Medical Building Associates, P.O. Box 369, Ellensburg, WA 98926.

PHYSICIANS WANTED

STAFF PSYCHIATRIST—Spokane Community Mental Health Center seeks board-eligible staff psychiatrist to join five full-time psychiatrists and large multidisciplinary staff. Varied duties include consultation, staff supervision, and direct service, primarily with chronically mentally ill. Programs for this population include Fountain-House-type club, medication clinics, and intensive short-term day programs. Spokane, in beautiful NW setting, population 348,000, is a low-cost-of-living area and superb place to raise family. Salary $59,000, plus excellent benefits. Inquire: Executive Director Mary Higgins or Dr Tad Patterson, Spokane CMHC, S. 107 Division, Spokane, WA 99202, or call collect, (509) 838-4651. EOE

UROLOGIST, ORTHOPAEDIC SURGEON, OBSTETRICIAN/GYNECOLOGIST AND NEUROLOGIST to join progressive multi-specialty clinic in sunny southeastern New Mexico. Modern facility, family oriented community of 40,000, service area 125,000. Good salary plus incentive bonus paid on production. Many excellent benefits including insurance, paid vacations and continuing education, stock option offered. Immediate openings, call (505) 392-5571, or send CV to Melba Greer, Recruiting Director, Norte Vista Medical Center, Ltd., 2410 North Fowler, Hobbs, NM 88240.

GENERAL PRACTITIONERS—Specialists—Full time positions or Locum Tenens. If You're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

OBSTETRICIAN AND GYNECOLOGIST, Southern California—Leading HMO with 28 facilities, 350,000 members and 370 full-time physicians in Los Angeles and Orange Counties has opportunities for OB/GYN specialists. Excellent compensation and benefits. Send curriculum vitae to Director/Physician Recruitment: CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

OBSTETRICIAN-GYNECOLOGIST to join 3-physican department in 28 member multispecialty group. Excellent hospital facilities. Drawing area 170,000. Unexcelled skiing and outdoor recreation. Fee-for-service practice with small HMO option. CV and two references to Mary Beard, MD, Ogden Clinic, 4650 Harrison, Ogden, Utah.

CALIFORNIA-URGENT CARE. Positions available for Fall 1984 in free-standing, urgent care settings in several locations. Board certification or eligibility in Emergency Medicine, Family Practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Ave, Suite 500, Oakland, CA 94610, (415) 832-6400.

CALIFORNIA, SAN JOSE: Established group has full and part-time positions available for physicians with experience in Emergency Medicine and Family Practice to staff Acute Care Clinic at teaching hospital and a new low-volume Emergency Department. Minimum Guarantee plus Fee-for-Service. Contact: James B. Lane, MD, 1625 The Alameda, #201, San Jose, CA 95126; Phone: (408) 293-8881.

(Continued on Page 418)

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SPECTRUM EMERGENCY CARE, Inc.

Career emergency medicine positions are available with the nation's largest group in the following states:

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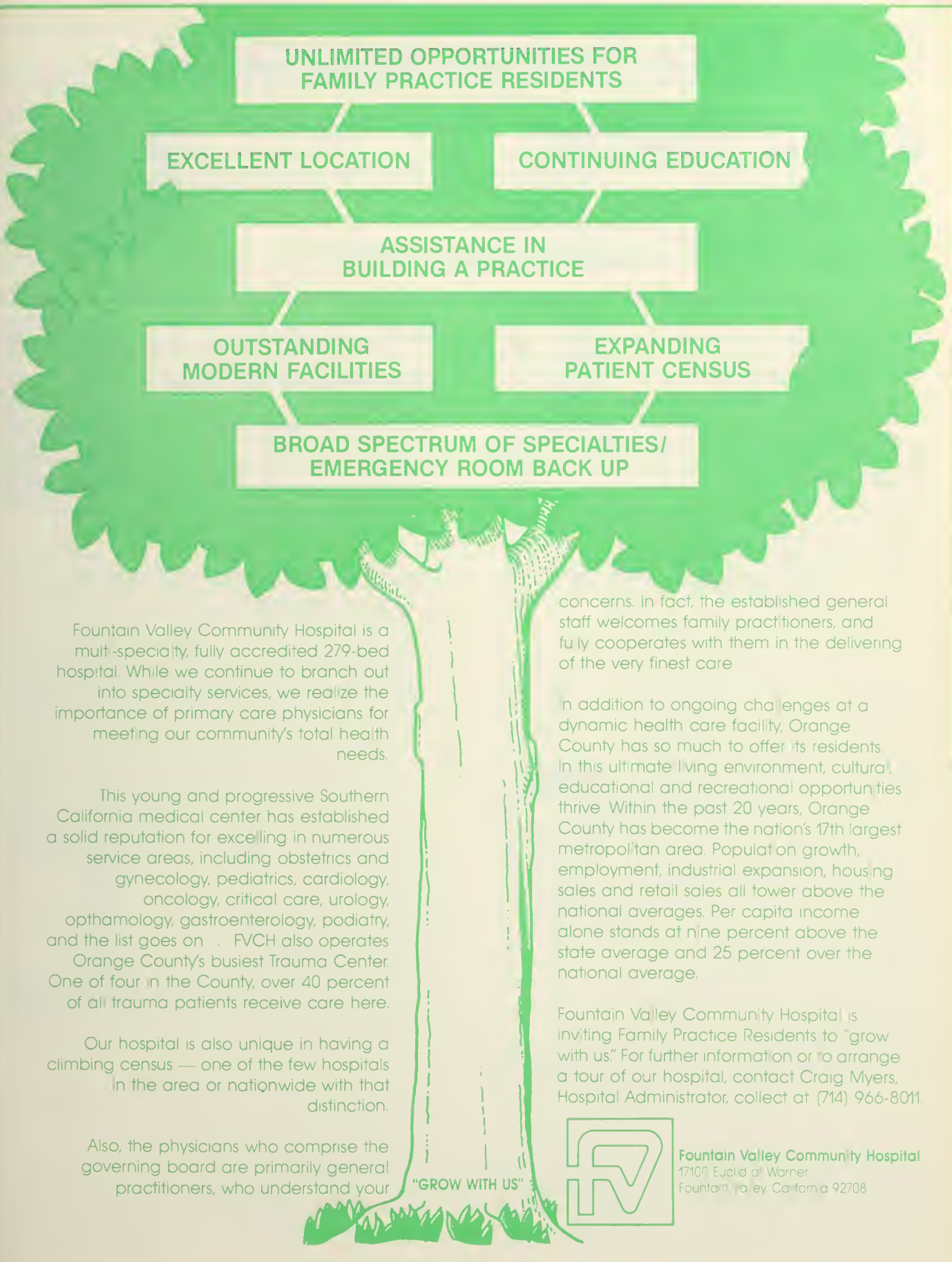
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BROAD SPECTRUM OF SPECIALTIES/ EMERGENCY ROOM BACK UP
"GROW WITH US"

Fountain Valley Community Hospital is a multi-specialty, fully accredited 279-bed hospital. While we continue to branch out into specialty services, we realize the importance of primary care physicians for meeting our community's total health needs.

This young and progressive Southern California medical center has established a solid reputation for excelling in numerous service areas, including obstetrics and gynecology, pediatrics, cardiology, oncology, critical care, urology, opthamology, gastroenterology, podiatry, and the list goes on . FVCH also operates Orange County's busiest Trauma Center. One of four in the County, over 40 percent of all trauma patients receive care here.

Our hospital is also unique in having a climbing census — one of the few hospitals in the area or nationwide with that distinction.

Also, the physicians who comprise the governing board are primarily general practitioners, who understand your concerns. In fact, the established general staff welcomes family practitioners, and fully cooperates with them in the delivering of the very finest care

In addition to ongoing challenges at a dynamic health care facility, Orange County has so much to offer its residents. In this ultimate living environment, cultural, educational and recreational opportunities thrive Within the past 20 years, Orange County has become the nation's 17th largest metropolitan area. Population growth, employment, industrial expansion, housing sales and retail sales all tower above the national averages. Per capita income alone stands at nine percent above the state average and 25 percent over the national average.

Fountain Valley Community Hospital is inviting Family Practice Residents to "grow with us." For further information or to arrange a tour of our hospital, contact Craig Myers, Hospital Administrator, collect at (714) 966-8011.

Fountain Valley Community Hospital
17100 Euclid at Warner
Fountain Valley, California 92708

Utah State Medical Association Annual Meeting

OCTOBER 3, 4, 5, 1984
HOTEL UTAH • SALT LAKE CITY

SCHEDULE

WEDNESDAY—OCTOBER 3

8:00 am	Continental Breakfast
8:30 am	House of Delegates Opening Session
10:30 am	Reference Committees
12:30 pm	Luncheon Speaker **HARRISON L. ROGERS, Jr, MD** *President-Elect,* *American Medical Association* **Changing Roles of Physicians and Hospitals**
2:00 pm	Reference Committees
3:00 pm	Hospital Medical Staff Section

THURSDAY—OCTOBER 4

7:30 am	Continental Breakfast
8:00 am	House of Delegates Election of Officers
9:00 am	**FORUM FOR MEDICAL ISSUES** **Perspectives in Medicine**
1:00 pm	Luncheon
2:00 pm	House of Delegates
6:30 pm	Presidents' Reception
7:30 pm	Presidents' Banquet

FRIDAY—OCTOBER 5

COMPUTERS IN MEDICINE

8:30 am to 4:30 pm	Computer Exhibits
9:00 am	Computers in the Physician's Office
10:00 am	Academic Information Systems and On-Line Database Use
11:00 am	Purchasing a Computer

FRIDAY—OCTOBER 5

Computers in Medicine

9:00 am—Computers in the Physician's Office

ROBERT J. FLAHERTY, MD, Bozeman, Montana. Dr Flaherty, a family physician and clinical assistant professor at the University of Utah, has written several software packages, published articles and spoken often about computers in medicine.

10:00 am—Academic Information Systems and On-Line Database Use

WAYNE J. PEAY directs the Computer and Media Services Department, Spencer S. Eccles Health Sciences Library, University of Utah. He is one of the principals in the Integrated Academic Information Management System (IAIMS) project at the University of Utah. He has given numerous presentations on academic information systems and microcomputers.

NINA E. DOUGHERTY directs the Information Services for the Spencer S. Eccles Health Sciences Library, University of Utah. She supervises the computer search service at the library and is familiar with NLM, BRS, DIALOG, SDC, INFOLINE, AMA/GTE and other systems. She provides demonstrations, training and comparative information for computer users.

11:00 am—Purchasing a Computer—Panel Discussion

Moderator: JOHN B. STANCHFIELD, MD, Salt Lake City. Dr Stanchfield has extensive experience with medical office computers and advises the American Society of Internal Medicine on physician office computers.

8:30 am to 4:30 pm—Vendor Exhibits

Local computer firms will display physician office systems.

Registration: No registration fee for USMA members
Non-members $50 • Thursday Luncheon $10 • Presidents' Banquet $50 per couple

CME Credit: Forum for Medical Issues and Computers in Medical Practice sessions approved for 7 hours CME credit.

THURSDAY, OCTOBER 4 • 9:00 AM-1:00 PM

FORUM FOR MEDICAL ISSUES
Focus on Perspectives in Medicine

Nationally prominent speakers will present a challenging and thought provoking session focusing on the rapid changes taking place in medicine today and the ethical dilemmas presented by these changes.

Ethics in Medicine, A Historical Perspective

PAUL BRUCE BEESON, MD

An emeritus professor of medicine at the University of Washington, Dr Beeson has had a distinguished career as a physician, professor and observer of medicine. He has been Professor of Medicine and Department Chairman for Emory University and Yale University and was a Nuffield Professor of Clinical Medicine at Oxford University, England.

Dr Beeson is a Fellow of the Royal College of Physicians and a Master of the American College of Physicians. He is the recipient of the John Phillips Memorial Award of the American College of Physicians, the Abraham Flexner Award of the Association of American Medical Colleges and Willard Thompson Award of the American Geriatrics Society. In 1981, Yale University created the Paul B. Beeson Professorship of Medicine.

Throughout his career, Dr Beeson has always been dedicated to quality medical education and has always maintained a warm and personal teaching style.

Ethics, Opportunities and Dilemmas of Research

CHASE N. PETERSON, MD

Dr Chase Peterson was recently appointed President of the University of Utah. His experience prior to this assignment includes a combination of medical practice and administrative positions. He graduated with honors from Harvard Medical School, completed an internship and residency in medicine and a fellowship in Metabolism/Endocrinology and Renal Disease. He then practiced medicine in Salt Lake City for five years. From 1967 to 1978 he served at Harvard University as Dean of Admissions and Financial aids and vice president for Alumni Affairs and Development. He returned to Utah in 1978 as vice president for Health Sciences at the University of Utah. In this position, he was responsible for the University Hospital, the School of Medicine, and colleges of health, pharmacy and nursing, which comprise about one third of the University's operations and one half of its research. He also served as the University coordinator for both the Study of Radiation Effects in Southern Utah and for the artificial heart project.

Redirecting Our Medical Research

ROBERT G. WILSON, MD

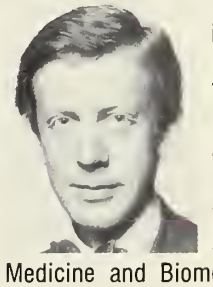
President of USMA in 1982-83, Dr Wilson initiated an effective medical cost containment effort for physicians in Utah. He started a grass roots study that resulted in the 1984 report adopted by the House of Delegates, "Medical Care Cost Containment Proposals." He is also the author of the "Economic Code of Medical Ethics" also adopted by Utah physicians.

Dr Wilson received the Salt Lake County Medical Society Award of Merit in 1980 for his work as Chairman of the Medical Ethics Committee. He also served on the Board of Directors for the Utah Health Cost Management Foundation.

After practicing medicine in Utah for 18 years, Dr Wilson recently moved to Prescott, Arizona, where he has a private practice in dermatology.

A Lawyer's Perspective on Hard Medical Choices

ALEXANDER MORAN CAPRON



Professor of Law, Ethics and Public Policy at Georgetown University. Alexander Moran Capron will become the first Topping Professor of Law, Medicine and Public Policy at the University of Southern California in January 1985.

Professor Capron served as the Executive Director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, a congressionally charged body that reported on a wide range of subjects in the area of bioethics and public policy.

In addition to his responsibilities for the 16 volumes issued by the President's Commission, Professor Capron has written or edited six books—including **Law, Science and Medicine** and **Catastrophic Diseases: Who Decides What?**—and more than 70 articles or chapters in professional journals, books and general publications.

Professor Capron has testified before committees of the Congress and state legislatures on many issues of public policy raised by the life sciences, ranging from genetic engineering and cancer research to organ replacement and the "definition" of death. His principal teaching and research interests are torts, the professions, and the social and legal aspects of medicine and science.

(Continued from Page 414)

PHYSICIANS WANTED

GENERAL/FAMILY PRACTICE

CIGNA Healthplans of California is offering a career opportunity to General and Family Practitioners with acute and preventive medicine orientation. Our HMO provides a personal patient population and a continuity of care as well as an excellent compensation package. Send curriculum vitae to:

Director Physician Recruitment

CIGNA Healthplans of California

700 N. Brand Blvd., Ste. 500
Glendale, CA 91203

Equal Opportunity Employer

FAMILY PRACTICE OPPORTUNITY. Established Family Practice group located in SW Washington, 15 minutes from Portland. Flexible scheduling Full partnership available within one year. Contact E. M. McAninch, MD at (206) 834-3141 or send CV to P.O. Box 1004, Camas, WA 98607.

MEDICAL DIRECTOR—For an innovative, cost containment program. Responsibilities include: planning, quality assurance and utilization review. Extensive interaction with local medical community. Clinical and administrative experience desired, preferably in a prepaid health plan. Arrangements to maintain clinical practice can be made. Send résumés to: Executive Recruitment Specialist, Monterey County Health Initiative, P.O. Box 221878, Carmel, CA 93922.

FAMILY PRACTITIONERS needed in northern California for practice incl. OB. Minimum $6,000/month, malpractice insurance and other benefits. Contact: Carol Sweig, Western Physicians Registry, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.

SAN FRANCISCO—1-year Fellowship in Psychosomatic Medicine and Consultation Liaison Psychiatry offered by St. Mary's Medical Center, a 550 bed private teaching hospital. Supervised clinical, teaching, and administrative experience in unique Med-Psych inpt unit, Med-Surg wards, Psychiatry and Medicine clinics, and Sleep Disorders Center. Board eligibility in Psychiatry or Medicine required. Contact: D. Nevins, MD, St. Mary's Medical Center, 450 Stanyan St, San Francisco, CA 94117.

CLINICAS DEL CAMINO REAL, INC. is seeking two FAMILY PRACTICE PHYSICIANS to augment its medical practice. Pay range is $4,200.00 to $5,000.00 per month plus share of inpatient work. Fringe benefits include 3 weeks vacation, sick leave, tax deferred annuity plan, 11 holidays and an excellent working environment. Located in Ventura County. Send résumé to Robert S. Juarez, Executive Director, P.O. Box 4878, Ventura, CA 93004. Bilingual Spanish/English desirable. An E.O.E.

FAMILY PRACTITIONER WANTED—Medium Sized, semi-urban, university community in the Willamette Valley—Western Oregon. Excellent location for outdoor activities. Well equipped hospital with complete specialty coverage. For further information, write or call collect: Stan Groth, Associate Administrator, McKenzie-Willamette Hospital, Springfield, Oregon 97477. Telephone: (503) 726-4404.

ESTABLISHED SOLO FAMILY PHYSICIAN in Malibu, California seeks board qualified/certified associate. Applicant must be responsible, humanistic and willing to develop the practice. Send CV to: MMC, 23440 Civic Center Way #102, Malibu, CA 90265.

CALIFORNIA, SAN FRANCISCO BAY AREA: Full-time career emergency physician wanted for high volume Emergency Department. Emergency Medicine Board Certified or Board-ready mandatory to participate in group of twenty full-time staff physicians seeing over 300 patients per day. Salaried position, excellent benefits include three weeks paid vacation; one week CME; paid malpractice, health, and life insurance; corporate shareholdership in three years. Send CV or contact William Green, MD or David Gallagher, MD, 27400 Hesperian Blvd., Hayward, California, 94541.

DIAGNOSTIC RADIOLOGIST: Board Certified preferably with post-graduate training or experience. Three person group with small hospital practice (CT & US). Expanding to offices in pleasant Sierra Foothills community, 35 miles east of Sacramento. Salary negotiable. CV with reply to Box 6440, Western Journal of Medicine, 44 Gough Street, San Francisco, CA 94103.

PHYSICIANS WANTED

DIRECTOR, FAMILY PRACTICE CENTER. Full-time faculty position available in the Department of Family Practice, University of California, Davis; Level of appointment commensurate with academic experience and credentials. Should be Board Certified by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research and academic publication activities. The position will remain open until filled; applications will not be accepted after 12/31/84. Send CV to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd., Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

DIRECTOR OF PREDOCTORAL FAMILY MEDICINE EDUCATION. Full-time faculty position available in the Department of Family Practice, University of California, Davis; level of appointment commensurate with academic experience and credentials. Should be Board Certified by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research and academic publication activities. The position will remain open until filled; applications will not be accepted after 12/31/84. Send CV to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd., Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer.

Internist

INTERNIST, Board certified or eligible. Excellent opportunity for private practice in Layton, Utah, 25 miles north of Salt Lake City. Ideal family location in community with patient population of approximately 96,000. Area served by Humana Hospital Davis North, a 110 bed, modern, full-service hospital. Benefits include paid on-site visit, moving expenses, assistance with office rent and a first year income guarantee. Inquire Humana Hospital Davis North, 1600 W. Antelope Drive, Layton, Utah 84041, or call collect (801) 825-9561, ext. 7008.

Humana Hospital Davis North

ASSISTANT PHYSICIAN—University of California, San Diego Comprehensive Health Center. Pediatric ambulatory care to newborns and children through age 18. California licensed MD with board certified in Pediatrics or eligibility for. $46,980 - $54,180 per annum plus excellent benefits. Staff position with eligibility for acad. appt. Apply ASAP to: UCSD, SPO, (14965-L) Q-016, La Jolla, CA 92093. AA/EOE Employer.

CHAIRPERSON, DEPARTMENT OF MEDICINE, SCHOOL OF MEDICINE, University of California, San Francisco, (UCSF)—Qualified candidates are invited to apply. Applicants should submit a curriculum vitae, bibliography and the names of four references to: Professor J. Michael Bishop, Chairman, Search Committee for Department of Medicine, Chairperson, c/o Ms. Valli McDougle, Dean's Office, School of Medicine, S-224, University of California, San Francisco, CA 94143. UCSF is an Affirmative Action/Equal Opportunity Employer. Women and minorities are urged to apply. Applications should be received by October 15, 1984.

NORTHERN CALIFORNIA: Physician, Board certified/qualified in Emergency Medicine or Family Practice, to work part-time or full-time in a busy free standing emergency center. Competitive compensation, malpractice, and bonus for part-time position. Full-time position will also include health insurance, vacation, educational expenses and other benefits. Send CV and references to Joanne Berkowitz, MD. The Emergency Center Medical Group, 4948 San Juan Avenue, Fair Oaks, CA 95628.

PARTNER NEEDED FOR REDWOOD CITY, CALIFORNIA PRACTICE: new ambulatory care clinic twenty-five miles south of San Francisco seeks BE/BC FP, IM, or EM physician. Ideal location opposite major new housing and retail development. No buy-in, guaranteed base compensation and incentive, regular hours. Send CV to Michael Goluska, MD, 2200 Sixth Ave., Suite 1200-BB, Seattle, WA 98121 or call collect (206) 624-6888.

GENERAL INTERNIST, BOARD CERTIFIED/eligible, Multispecialty group. Replace retiring Physician. Prime recreation area. Send résumé to: Dr. Bryan Stone, Box 2198, Ketchum, Idaho 83340 or call (208) 726-9361.

PHYSICIANS WANTED

LA JOLLA, CALIFORNIA-PULMONOLOGIST needed to join pulmonary-critical care group. Salary and later partnership or early buy-in. Must be BE/BC. Send CV to Box 6444, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

UNIVERSITY OF WYOMING STUDENT HEALTH SERVICE—The Student Health Service has an opening for a full-time physician beginning July 1, 1984. The physician must be Board Certified in Family Practice and have approved resident training or have extensive practice experience. Applicant must be licensed in the State of Wyoming and have at least four years of primary care experience. Physician to join three full-time and three part-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, pharmacy and infirmary. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity-Affirmative Action Employer. Send CV to: Dale C. Brentlinger, MD, Director, Student Health Service, University of Wyoming, University Station Box 3068, Laramie, Wyoming 82071.

FAMILY PRACTITIONER—TULARE COUNTY, CALIFORNIA—Board certified Family Practitioner to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $75,779-$79,639 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291, (209) 733-6266, An Affirmative Action Employer.

CALIFORNIA, SAN FRANCISCO—Experienced Emergency Department Director wanted for a moderate volume unit. Marketing experience or interest is necessary. Annual salary $60,000+. Send CV to: Emergency Physicians' Medical Group, 1 Maritime Plaza Suite 710, San Francisco, CA 94111.

UNEXPECTED OPPORTUNITY FOR INTERNIST to associate with three busy internists in suburban community 20 minutes east of San Francisco. Reply with CV to Box: 6443, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

GENERAL PRACTITIONER/INTERNIST—excellent opportunity for young physician in sunny east San Francisco Bay area—25 miles fro San Francisco. Contact Carol Bull, 1300 Bancroft Ave., San Leandro, CA 94577.

NEUROLOGIST/NEUROSURGEON (Board Certified)—For full- or part-time work with a Disability Evaluation facility. Send Curriculum Vitae to: Manager, 1127 Wilshire Blvd., Suite 1209, Los Angeles, CA 90017.

PULMONOLOGIST, Boarded Int. Med. and Board Eligible Pulmonology, to join 42-member multi-specialty group located on the Central Coast of California. Premium location, excellent practice opportunity with fully paid benefit and retirement program; guaranteed salary first six months followed by incentive pay program; all practice costs paid. For more information contact: Daniel Small, MD, Medical Director or David Graham, Assistant Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401.

PRACTICE WANTED

PRACTICE WANTED: Board Ccertified Internist wants to buy medical practice in California, town of 20,000 or more population. P.O. Box 6418, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

SITUATIONS WANTED

DIAGNOSTIC RADIOLOGIST desires situation in small hospital (25-50 beds) CT and Ultrasound (real time). Willing to do some locums. Licensed in California, Oregon and Washington. Please reply Box 6436, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

LEGAL COUNSEL

BMQA

Former Deputy Atty. General representing BMQA & Dept. of Health Now specializing in BMQA investigations and disciplinary actions. Hospital Staff Privilege cases and Defense Malpractice cases thruout Calif.

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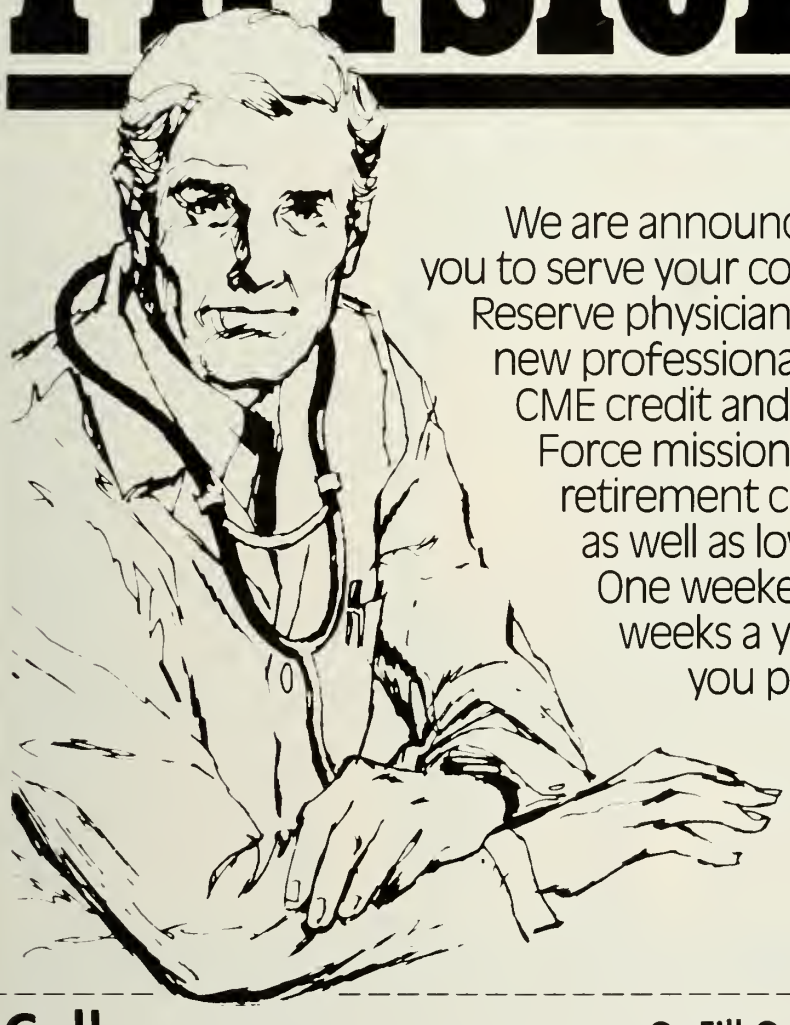
(Continued on Page 420)

PHYSICIANS



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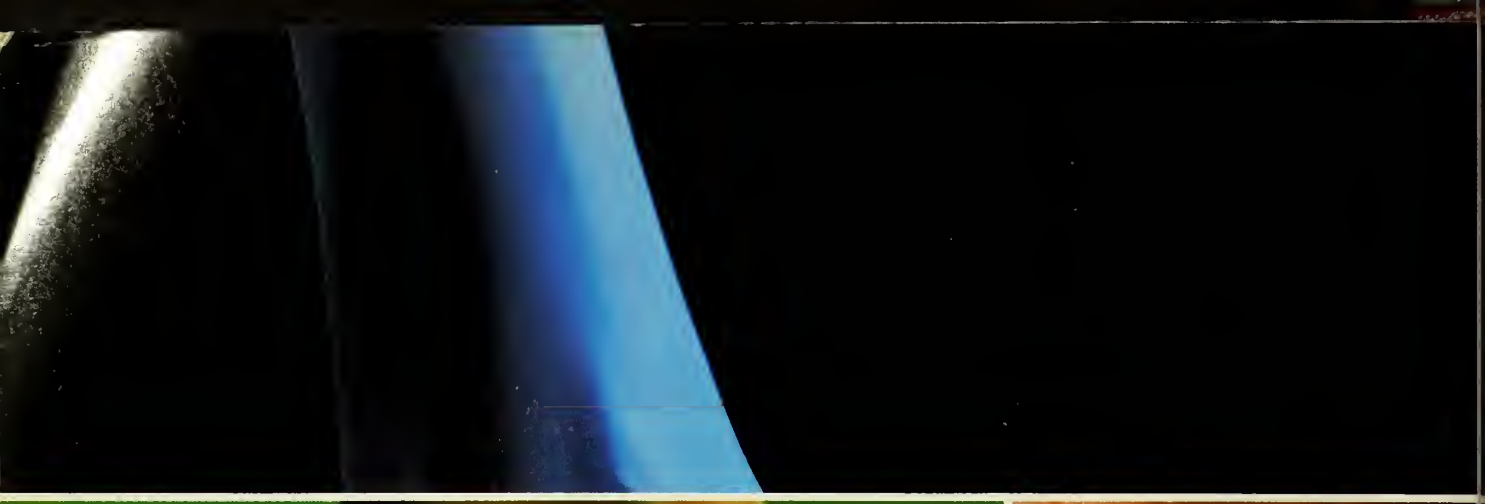

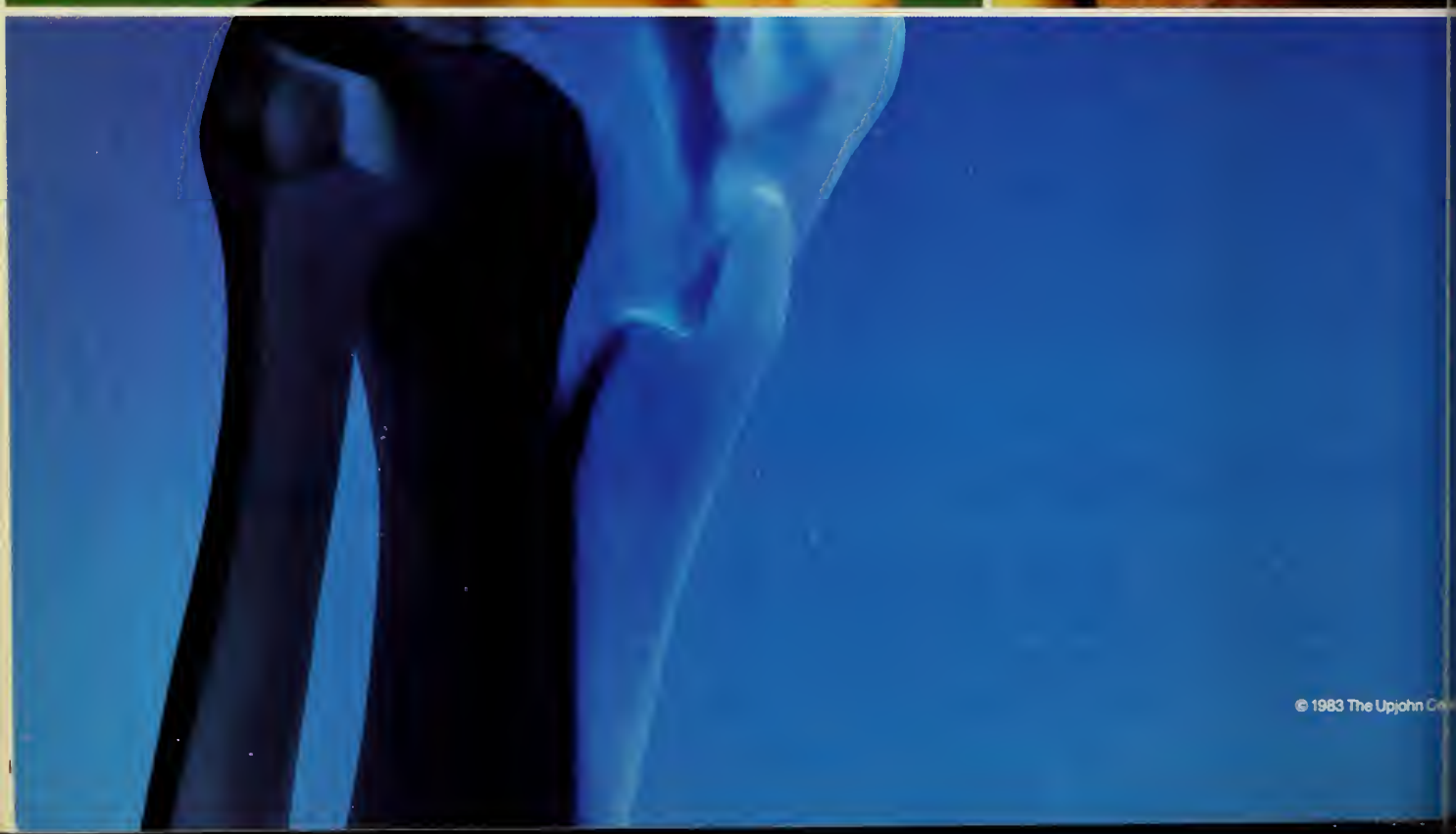

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Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

Advanced age has little or no influence on the pharmacokinetics of *Motrin.*

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

Helping you to help your patients—
Ask your Upjohn Representative for a complimentary supply.

The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS (ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

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Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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Doctors Won Independence With SCPIE

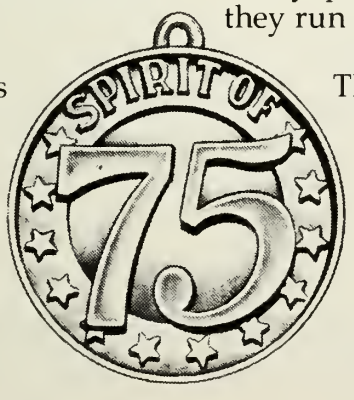
The situation was grim in 1975.
The cost of professional liability insurance had skyrocketed nearly 500% in 6 years. Most commercial carriers quit the field, and those remaining wanted more than doctors and their patients could pay.

Bombarded by nuisance lawsuits and runaway jury verdicts, doctors faced an historic crisis.

That's when the Spirit of '75 took hold.
Doctors fought back—and won!
First, the Legislature passed a law to control lawsuit mania.

Then came the real key to victory—physicians organized their own insurance company—SCPIE.

Today, physician policyholders own SCPIE, they run it and they realize any profits.



The battle isn't over. SCPIE's success attracts many predators. But physicians will keep their independence as long as they support their company.

That's the Spirit of '75!

scpie

Sponsored by SOCAP: The medical associations and societies of Kern County, Los Angeles County, Orange County, San Bernardino County, San Luis Obispo County, Santa Barbara County and Ventura County.

Southern California Physicians Insurance Exchange, 2029 Century Park East, Las Angeles, CA 90067 (213) 552-8900

(Continued from Page 412)

October 12-14—**28th Annual Western Occupational Health Conference.** Western Occupational Medical Association at Holiday Inn Golden Gateway, San Francisco. Friday-Sunday. 10 hrs. Contact: Joe Donovan, c/o WOMA, 433 Palmer Ave., Aptos 95001. (408) 688-0667.

October 15-18—**9th Annual Family Practice Update.** LLU. Monday-Thursday.

October 16-18—**Primary Medical Care of Selected Infectious Diseases.** Health Science Seminars of UCSF at Sheraton Hotel, Poipu Beach, Kauai, HI. Tuesday-Thursday. $225. Contact: Cynthia Vaughan, Program Coordinator, PO Box 22023, San Francisco 94122. (415) 861-2713.

October 17—**Second Annual Alcohol & Drug Dependencies Symposium.** Kaiser Permanente Southern California at The Pasadena Hilton, Pasadena. Wednesday. $90. Contact: Judy Harrison—Dept. of Clinical Services, Kaiser-Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 18-21—**Clinical Biofeedback Certificate Program.** UCLA. Thursday-Sunday.

October 19-21—**Medical Mycology.** UCSF. Friday-Saturday.

October 22-25—**Primary Care Update: 69th Scientific Assembly of Interstate Postgraduate Medical Association** at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: H. B. Maroney, (608) 257-6781.

October 25-27—**Postgraduate Institute.** CMA at Monterey Sheraton, Monterey. Thursday-Saturday. $150—Non-member, $100—Member. Contact: Janice Rigney (415) 863-5522 Ext. 416.

October 26-28—**Weekend Workshop on Stress for Physicians and Spouses.** CMA at Holiday Inn, Napa. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

October 29-November 1—**Interstate Postgraduate Medical Association Meeting** at Las Vegas. Monday-Thursday. Contact: H. B. Maroney, Exec. Dir., PO Box 1109, Madison, WI 53701. (608) 257-6781.

November 9—**New Concepts in Medicine—20th Annual Staff Seminar.** California Hospital Medical Center, Los Angeles. Friday. (213) 748-2411.

November 9-11—**Hawaii Medical Association Annual Meeting** at Kauai Surf Hotel, Kauai. Friday-Sunday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu, HI 96814. (808) 536-7702.

November 10—**Infectious Disease.** UCD at Holiday Inn Holidome, Sacramento. Saturday.

November 18—**16th Annual Symposium: "The Newest Concepts in Clinical Practice."** Granada Hills Community Hospital & UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Carol Smith, Granada Hills. (818) 360-1021.

November 30-December 2—**Weekend Workshops on Stress for Physicians and Spouses.** CMA at La Playa Hotel, Carmel. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

IDAHO

October 18-24—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** Fishing and Chukar hunting adventure on the Main Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

September 21-22—**American College of Physicians—Regional Meeting.** Heritage Inn, Great Falls. Friday-Saturday. Contact: Warren D. Bowman, Jr, MD, Billings Clinic, Box 2555, Billings 59103.

October 4-6—**Montana Medical Association Annual Meeting.** Sheraton, Billings. Thursday-Saturday. Contact: MMA, 2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Com-

(Continued on Page 426)

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(Continued from Page 424)

mittee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 3-6—**Annual Microsurgery Workshop.** Albuquerque. Wednesday-Saturday. UNM School of Medicine, Basic Medical Sciences Building. 28 hrs. NM and AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

October 4-6—**The 12 Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Savage Auditorium, Presbyterian Professional Building. 23 hrs. AMA and NM Cat. I. Contact: The New Mexico Heart Institute, 201 Cedar SE, #604, Albuquerque 87106. (505) 242-2796.

October 26—**Practice Marketing Techniques.** Albuquerque. Friday. Savage Auditorium, Presbyterian Professional Building. Contact: NM Society of Internal Medicine, 303 San Mateo NE, Ste. 204, Albuquerque 87108. (505) 266-7868.

October 27—**Computers in Medical Practice.** Albuquerque. Saturday. Savage Auditorium, Presbyterian Professional Building. Contact: NM Society of Internal Medicine, 303 San Mateo NE, Ste. 204, Albuquerque 87108. (505) 266-7868.

November 2—**Los Alamos Cancer Center Annual Program.** Los Alamos. Friday. Credit hours pending. Contact: Los Alamos Cancer Center, Los Alamos 87544. (505) 662-9620.

November 9-10—**New Mexico Medical Society Interim Meeting—Sports Medicine.** Clovis. Friday-Saturday. 6 hrs. AMA and NM Cat. I. Contact: NMMS, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 14-15—**ABCs of Chronic Pulmonary Disease in Children and Young Adults.** Albuquerque. Wednesday-Thursday. Savage Auditorium, Presbyterian Professional Building. 14 hrs. NM Cat. I. Contact: Roy Goddard, MD, Winrock Medical Center, Albuquerque 87110. (505) 883-8246.

November 15-16—**ABC's of Chronic Lung Disease in Infants, Children and Young Adults.** Albuquerque. Thursday-Friday. 17 hrs. NM and AMA Cat. I. Contact: Winrock Medical Plaza Pediatric Pulmonary Center, 7400 Indian School Rd. NE, Albuquerque 87110. (505) 883-8217.

November 30-December 1—**Trauma Update 84.** Albuquerque. Friday-Saturday. Albuquerque Convention Center/Regent Hotel. 11 hrs. NM and AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

January 23-27—**New Mexico Metabolism Symposium.** Taos. Wednesday-Sunday. Tennis Ranch. 12 hrs. NM and AMA Cat. I. Contact: Office of CME, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87106. (505) 262-7353.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. NM and AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

CONTINUING MEDICAL EDUCATION

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

SKELETAL MUSCLE PATHOLOGY—Edited by Frank L. Mastaglia, MD-(WA), FRACP, FRCP, Associate Professor of Neurology, University of Western Australia, and Consultant Neurologist, Queen Elizabeth II Medical Center, Perth; and Sir John Walton, TD, MD, DSc, FRCP, Professor of Neurology, University of Newcastle upon Tyne, and Consultant Neurologist, Newcastle Area Hospitals, England. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 630 pages, $95.00.

SOC TRANG—A VIETNAMESE ODYSSEY—Carl E. Bartecchi, MD, Associate Clinical Professor, Department of Medicine, University of Colorado Medical School, Denver. Rocky Mountain Writers Guild, Inc., 2969 Baseline Rd., Boulder, CO 80303, 1982. 201 pages, $4.95 (paperback).

SO YOU WANT TO BE A SURGEON . . . —2nd Edition—David M. Heimbach, MD, and Kaj Johansen, MD, PhD, Department of Surgery, University of Washington School of Medicine, Seattle, 1983. 162 pages, $7.00 (softbound).

SPECIFIC HEART MUSCLE DISEASE—Edited by Cecil Symons, MD, FRCP, Consultant Physician and Cardiologist, Tom Evans, MB, ChB, FRCP, FACC, Consultant Cardiologist, and Andrew G. Mitchell, BA, BM, BCh, MRCP, Senior Registrar in Cardiology, Royal Free Hospital, London. John Wright • PSG, Inc., 545 Great Rd., Littleton, MA 01460, 1983. 139 pages, $25.00.

SPORTS MEDICINE—Fitness, Training, Injuries—Second Edition—Edited by Otto Appenzeller, MD, PhD, Professor of Neurology and Medicine, and Ruth Atkinson, MD, Associate Professor of Neurology end Pediatrics, University of New Mexico School of Medicine, Albuquerque. Urban & Schwarzenberg, 7 E. Redwood St., Baltimore, MD 21202, 1983. 434 pages, $24.50 (softbound).

STEROIDS IN ASTHMA: A REAPPRAISAL IN THE LIGHT OF INHALATION THERAPY—Edited by T. J. H. Clark, Professor of Thoracic Medicine, Guy's Hospital Medical School, London. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 233 pages, $42.50.

SUDDEN CARDIAC DEATH IN THE COMMUNITY—Contributing Editors: Mickey S. Eisenberg, MD, PhD, Associate Professor, Department of Medicine; Lawrence Bergner, MD, MPH, Affiliate Professor, Dept of Health Services; Alfred P. Hallstrom, PhD, Research Associate Program, Dept of Biostatistics, University of Washington; Thomas Hearne, PhD, Program Analyst, King County Division of Emergency Medical Services, Seattle; William B. Carter, PhD, Associate Professor, Dept of Health Services, and Richard O. Cummins, MD, MPH, MSc, Assistant Professor, Dept of Medicine, University of Washington, and Judith Pierce, MA, Manager, King County Division of Emergency Medical Services, Seattle. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1984. 163 pages, $27.95.

SURGERY OF THE KNEE—Edited by John N. Insall, MD, Professor of Orthopedic Surgery, Cornell University Medical Center; Attending Orthopedic Surgeon, The Hospital for Special Surgery and The New York Hospital; Chief of the Knee Service, The Hospital for Special Surgery, New York, and Honorary Consultant Surgeon, The London Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 807 pages, $95.00.

TEXTBOOK OF CYSTIC FIBROSIS—John D. Lloyd-Still, MD, Associate Professor of Pediatrics, Northwestern University, Director of the Cystic Fibrosis Center and Head of the Division of Gastroenterology, Children's Memorial Hospital, Chicago. John Wright • PSG Inc., Littleton, MA 01460, 1983. 476 pages, $67.50.

TEXTBOOK OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY—Edited by James V. Talano, MD, Chief, Cardiac Graphics Laboratory, Northwestern Memorial Hospital, and Associate Professor of Medicine, Northwestern University Medical School, Chicago; and Julius M. Gardin, MD, Acting Chief, Cardiovascular Section, VA Medical Center, Long Beach, Calif, Director, Cardiology Noninvasive Laboratory and Asst Professor of Medicine, University of California, Irvine. Grune & Stratton, Inc., 111 Fifth Ave, New York, NY 10003, 1983. 420 pages, $45.00.

ULTRASONIC SECTIONAL ANATOMY—Edited by Patricia Morley, MB, BS, DMRD, FRCP, Consultant Radiologist, Ultrasonic Unit, Department of Diagnostic Radiology, and Gabriel Donald, DA, FMAA, Senior Lecturer, Department of Medical Illustration, Western Infirmary, Glasgow, Scotland; and Roger Sanders, MD, Associate Professor, Department of Radiology and Radiological Sciences, The Johns Hopkins Hospital, Baltimore. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 226 pages, $69.00.

ULTRASONICS IN CLINICAL DIAGNOSIS—Third Edition—Edited by B. B. Goldberg, MD, Division of Ultrasound and Radiologic Imaging, Thomas Jefferson University Hospital, Philadelphia, and P. N. T. Wells, PhD, Department of Medical Physics, Bristol General Hospital, Bristol, United Kingdom. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1983. 236 pages, $35.00, (softbound).

ULTRASOUND IN INFLAMMATORY DISEASE—Volume 11 in Clinics in Diagnostic Ultrasound—Edited by Anton E. A. Joseph, MSc, MB, BS, FRCP, Consultant Radiologist and Head, Department of Nuclear Medicine and Ultrasound, St. George's Hospital, London, and David O. Cosgrove, MA, MSc, MRCP, Consultant in Nuclear Medicine and Ultrasound, The Royal Marsden Hospital, Sutton, Surrey, England. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 268 pages, $30.00.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * *

CARDIOLOGY

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OMSU-CME.

EMERGENCY MEDICINE

November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

NEONATAL MEDICINE

September 22-23—**Symposium on Neonatal Medicine.** Portland. Saturday-Sunday. Marriott Hotel. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

November 30-December 1—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses In Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

(Continued on Page 430)

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LOCUM TENENS

WORK PART TIME: Position available for Internist or GP with internal medicine experience to work at Primary Care Practice in Northern California Sierra foothills community of 25,000, 70 miles North of Sacramento. Share rotating practice with two other MD's; you work 1 week in 3. Out-patient and in-patient responsibilities in modern, fully equipped hospital. Minimum salary of 2,000./week plus incentives. Insurance and housing provided. Send CV and references to: David Lomba, Business Manager—133 'A' Ascot Ct., Moraga, CA 94556.

GENERAL RADIOLOGIST seeks ½-time position in South Bay (S.F.). Experienced in routine diagnostic studies plus industrial injury—acute care cases. Reply to Box 6442, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PART TIME PHYSICIAN NEEDED at San Francisco Health and Fitness Center. Must have knowledge in preventive medicine, fitness, exercise testing and have supportive lifestyle. Call Patrice Rossi, PHYSIS INC. (415) 781-6400.

LOCUM TENENS SERVICE
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. . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

OFFICE SPACE FOR SALE OR LEASE

MEDICAL OFFICE SPACE available for lease. 1,075 sq ft in Berkeley near Alta Bates. Please call The Berkeley Central Medical Building at (415) 848-5137.

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SILICON VALLEY—Space available in multi-disciplinary,well-run,computerized office near hospital. High income,high growth region. Rent on percentage basis possible. Kenneth Peters, MD, 515 South Dr., Suite 15, Mountain View,CA 94040; (415) 961-9430.

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ORTHOPAEDIC PRACTICE, ORANGE COUNTY, CALIFORNIA, adjacent to major hospital, five additional hospitals in 5-mile radius, will aid in transition. Box 4191, Irvine, CA 92714.

ALLERGY, SAN FRANCISCO BAY area. Seller plans to retire at end of 1984. 85% of practice concerns environmentally induced illnesses, 15% Forensic Medicine. Buyer must be Board certified in Allergy and Immunology or Toxicology and have extensive post graduate training and experience in clinical ecology. Strong research and academic background essential. Income has averaged 450-K over the past 5 years. Easy terms. For further information please write Box 6437, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE OPPORTUNITY in beautiful rural community in Sierra foothills. Close to large metropolitan areas and mountains. Excellent recreational opportunities. Close proximity to hospital. Good call coverage. Send inquiries to Box 6439, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103

SOUTHERN CALIFORNIA FAMILY MEDICAL PRACTICE FOR SALE. Idyllic location near ocean in beautiful Santa Barbara. Gross $150,000. Physician owner must leave country for family reasons. Call (805) 967-9668 or (805) 965-4531.

CALIFORNIA AND WESTERN STATES. HIGH INCOME practices for sale: Ophthalmology, Orthopedics, Radiology, OB/GYN, Psychiatry, Internal, Family, Pediatric, others. Mary Bradshaw, Professional Practice Opportunities, 21 Altamount Drive, Orinda, CA 94563; (415) 376-0762. Sales, Appraisals, Consulting, Placement, Résumé preparation service.

INTERNIST—Board certified to share established (growing) Internal Medicine (Inf. Dis. Spec.) practice. Good recreational area, 45 minutes from Sacramento. Send CV to Box 6441, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

UNIQUE SURGICAL OPPORTUNITY—requires certified old-fashioned broad-coverage general surgical experience—some trauma and light industrial injury expertise combined with desire to move with family to economically strong town in N.E. Wyoming. No unemployment, no welfare problems! New perfectly equipped 130 bed hospital with medical staff of 30 in almost all specialities. Three local surgeons—one leaving for personal reasons with active $230,000 gross 9 year established solo practice in well located $185,000 building. A reasonable real estate investment in growing medical community. Practice available at no cost for purchase of building on convenient terms. Will remain long enough to help establish replacement and continuity of practice. Call (307) 686-3840.

OTORHINOLARYNGOLOGY—Excellent private practice opportunity in Caldwell, Idaho, a community of 18,000 with service area population of 145,000. A well equipped 150 bed HCA hospital services this area which affords an abundance of recreational activities for all seasons. For further details, contact Jim Hudnall at (800) 527-0735 or collect (214) 644-2600.

FOR SALE—GYN practice—1840 charts. Albuquerque. Reasonable price/terms. For appraisal call/write RH Medical Group, 12651 Briar Forest #180, Houston, TX 77077; (713) 496-7777.

PRACTICES AVAILABLE

SAN DIEGO PEDIATRIC PRACTICE. Lucrative and well-established. Fully equipped modern office in excellent location. Average 5-year profits exceed 67%. Asking Price: $100,000. For details contact H.A. Coates, Medical Management Consultant, P.O. Box 2711, La Mesa, CA 92041 or call (619) 461-1367.

WENATCHEE, WASHINGTON FAMILY PRACTICE: Physician retiring after 40 years. Fully equipped office and nurse to remain to insure success. Beautiful location summer and winter. Outstanding medical facilities in city. Contact—Dr. R.E. Bolton at (509) 662-8213 or 662-8117.

SERVICES AVAILABLE

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MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 AM. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

September 21-22—**Unresolved Grief and Transgenerational Family Therapy** (Sponsor: University of Utah). Friday-Saturday. Snowbird. 12 hrs. Fee to be announced. Contact: Marsha Stroup, PhD, (801) 278-9141.

November 30—**Sleep Disorders: A Clinical Approach** (Sponsor: University of Utah/Pulmonary Division, LDS Hospital). Friday. Marriott Hotel, Salt Lake City. Credit and fee to be announced. Contact: DuWayne Schmidt, MD, (801) 321-1100.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 15-16—**Soft Tissue Surgery.** Seattle. Saturday-Sunday. U/W Health Sciences. Contact: U/W.

September 26—**Advances in Lab Medicine.** Seattle. Wednesday. Health Sciences Center. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

October 3-5—**Molecular Medicine.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

October 5—**Practical Pulmonary Function.** Seattle. Friday. Contact: VMMC.

October 12—**Frontiers in Eye Care for the Allied Professional.** Seattle. Friday. Contact: VMMC.

October 12-13—**Neurology Update.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

October 13—**Radiology Northwest.** Saturday. U/W Health Sciences Center. Contact: U/W.

October 19—**Annual Cancer Conference: Early Screening and Detection.** Seattle. Friday. Contact: VMMC.

October 20—**Medical Alumni Day.** Seattle. U/W Health Sciences. Contact: U/W.

October 25-26—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Museum of History and Industry. Contact: U/W.

November 1-2—**Washington Chapter—American College of Emergency Physicians.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, WACEP, 2033 Sixth Avenue, #900, Seattle 98121. (206) 623-4801.

November 1-2—**Drug Therapy.** Seattle. Thursday-Friday . HUB-Upper Campus. Contact: U/W.

November 2-3—**Asbestos Related Lung Disease.** Seattle. Friday-Saturday. Contact: Ed Oshiro, Medical Education, Group Health Cooperative, 201 16th Ave E, Seattle 98112. (206) 326-7348.

November 8-9—**Alzheimers.** Seattle. Thursday-Friday. Westin. Contact: U/W.

November 9—**GI Update.** Seattle. Friday. Contact: VMMC.

November 9-10—**Microcomputers in Rehabilitation.** Seattle. Friday-Saturday. U/W Health Sciences. Contact: U/W.

November 14-16—**Hyperthermia in Cancer Therapy.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

November 17-24—(HAWAII) **Medicine and Society in History.** One week. Inter-Continental Maui, Maui. Contact: U/W.

November 29-30—**Organ Failure and Organ Transplantation.** Seattle. Thursday-Friday. Mayflower Park Hotel. Contact: U/W.

December 1—**Radiology for Attorneys.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

December 6-7—**Aging and Elderly.** Seattle. Thursday-Friday. Westin. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Friday. Contact: VMMC.

December 8—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

December 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

December 26-January 2—(HAWAII) **Medicine, Magic and Religion.** Maui. Wednesday-Wednesday. Royal Lahaina. Contact: U/W.

January 11—**Treatable Hepato-Biliary Disease.** Seattle. Friday. Contact: VMMC.

January 24-26—**Annual President's Meeting—Modern Ophthalmic Technology.** Washington State Academy of Ophthalmology at Seattle. Thursday-Saturday. Westin. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

January 31-February 1—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin. Contact: U/W.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 16—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

February 16-23—(IDAHO) **Internal Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

February 23-March 2—(IDAHO) **Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 2-9—(HAWAII) **Medicine in China.** Kauai. Saturday-Saturday. Royal Waikola. Contact: U/W.

March 2-9—(HAWAII) **Electromyography.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 9-16—(HAWAII) **Imaging for Non-Radiologists.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

March 23—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

March 23-30—(HAWAII) **Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 28-29—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences. Contact: U/W.

March 30-April 6—(HAWAII) **Neurology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 11-12—**DRG. Seattle. Thursday-Friday.** Westin. Contact: U/W.

April 13—**Handicapped Infant.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

April 18-19—**Death Investigation.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

May 2-3—**Exercising Women.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 15-17—**Infections Diseases.** Seattle. Wednesday-Friday. Westin. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin Hotel. Contact. U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

June 15—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W. WJM

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 8-11, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and Country, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 20-22, 1984, Mark Marriott, Vail.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: November 9-11, 1984, Kauai Surf Hotel, Kauai.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1985—date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: October 4-6, 1984, Sheraton, Billings.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: November 2-4, 1984, OMA Headquarters, Portland (House of Delegates).

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: October 3-5, 1984, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 13-16, 1984, Westin Hotel, Seattle.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1985—date and place to be announced.

ADVERTISING INDEX

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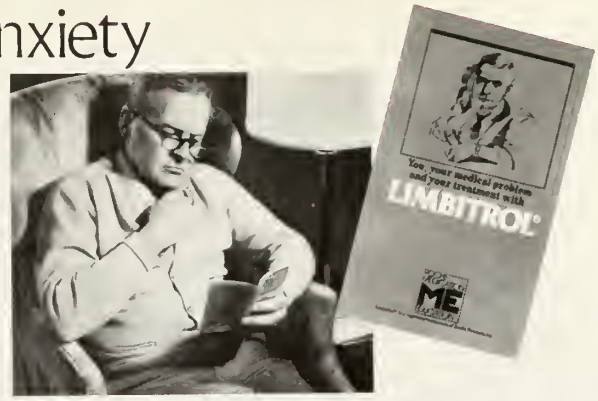
*Feighner JP: *Psychopharmacology* 61 217-225, Mar 22, 1979.



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Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do ot use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is chieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500. Tel-E-Dose® packages of 100. Prescription Paks of 50.

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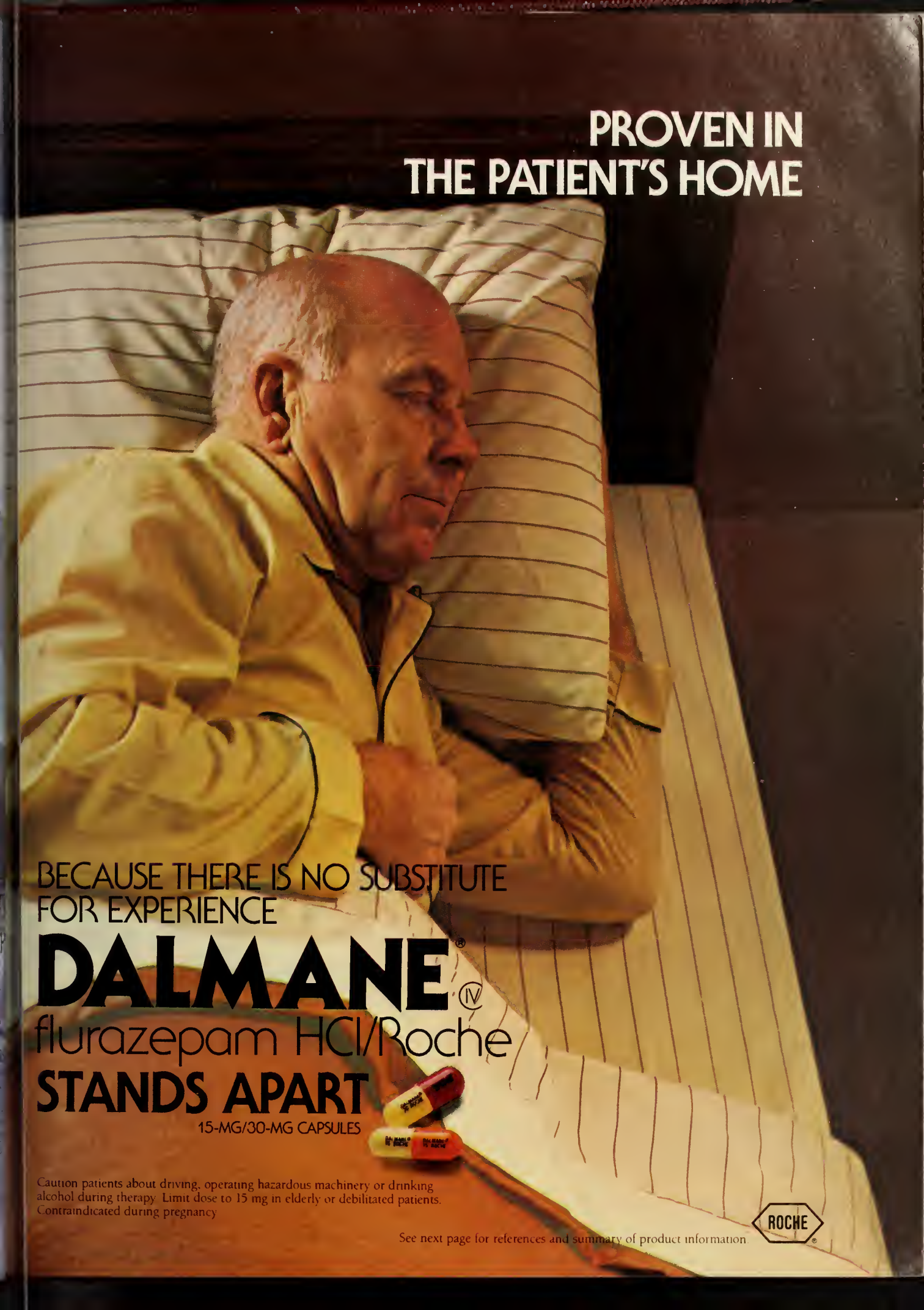
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Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

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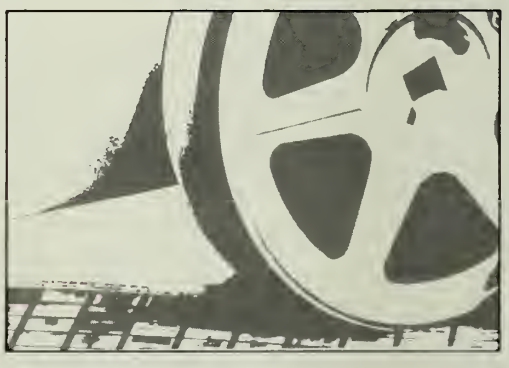

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Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

SQUIBB

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Princeton, NJ 08540 524-503
Issued: January 1984

ACE* INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis — Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on adjacent page)

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ACE* INHIBITOR

Capoten®
(captopril tablets)

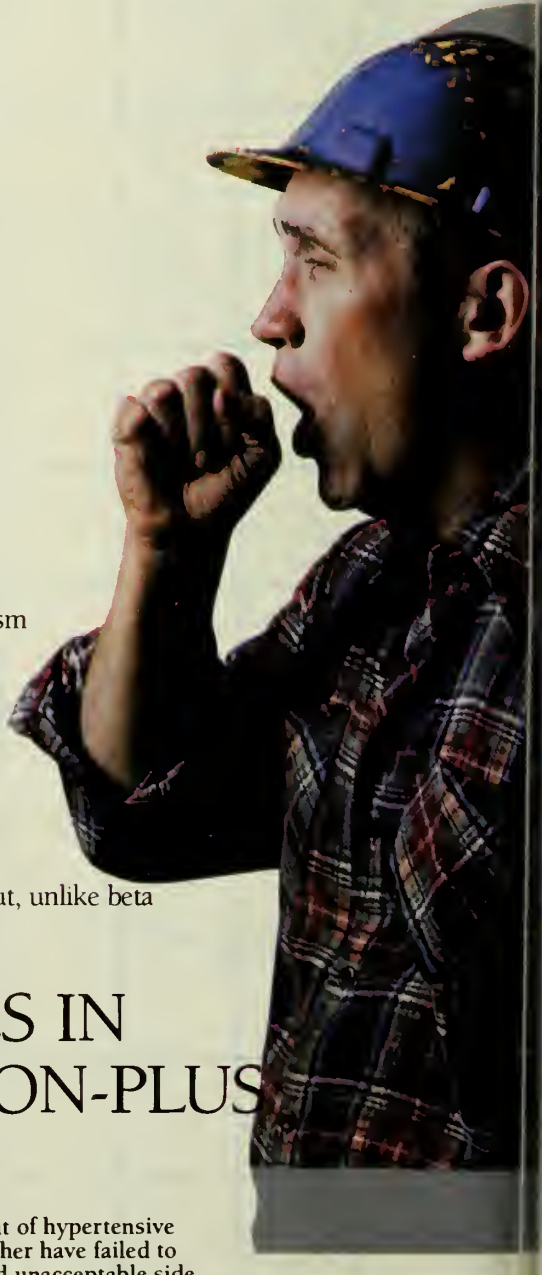
SQUIBB

FOR HYPERTENSION†-PLUS

Patients treated for hypertension† may have other disorders that commonly coexist with elevated blood pressure—approximately 14% may have diabetes, 7% asthma, 13% heart failure.[1] Unlike many other antihypertensive agents, CAPOTEN, because of its unique mode of action, is not contraindicated for use in any of these coexisting conditions that frequently complicate hypertension management:

+ DIABETES† (14%)

CAPOTEN does not mask the warning symptoms of hypoglycemia, unlike some beta blockers



+ BRONCHOSPASTIC PULMONARY DISEASE† (7%)

CAPOTEN rarely causes bronchospasm

+ HEART FAILURE† (13%)

CAPOTEN improves cardiac output, unlike beta blockers

MORE PLUSES IN HYPERTENSION-PLUS

*Angiotensin Converting Enzyme

†CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.

Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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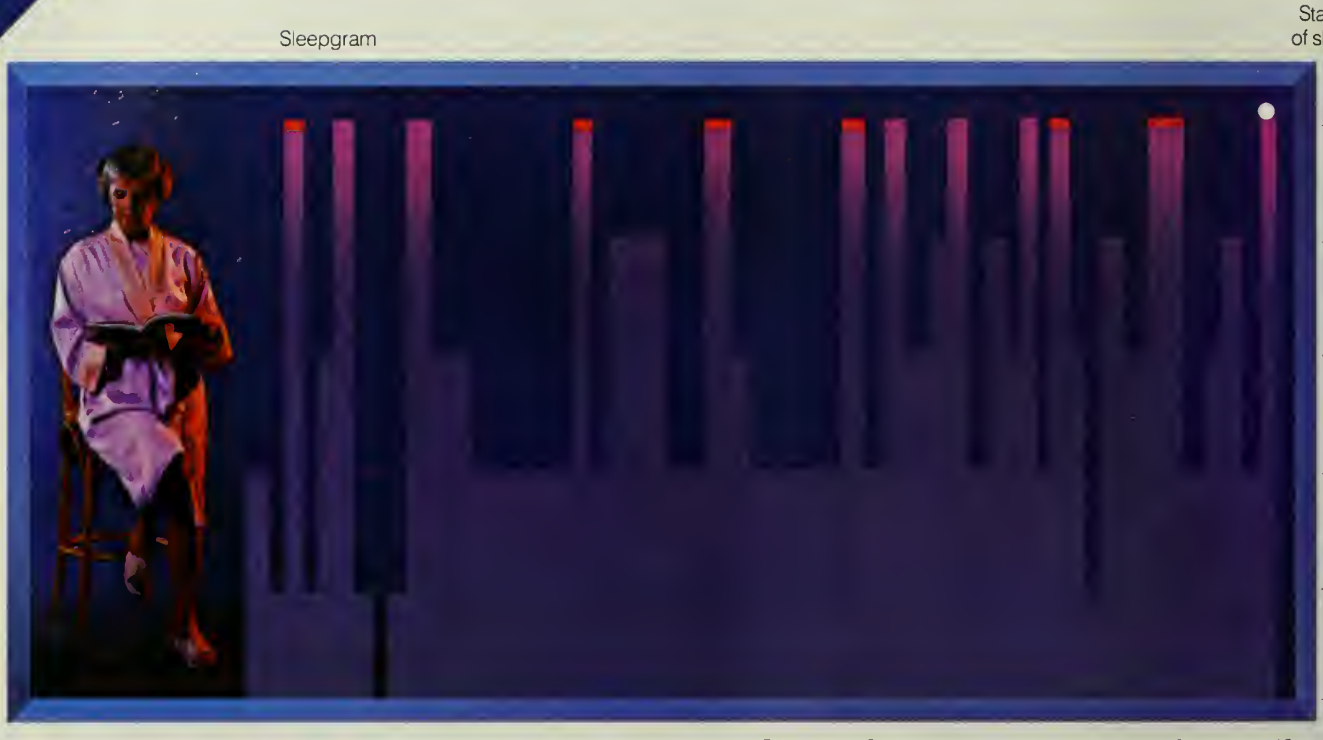
0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

= objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

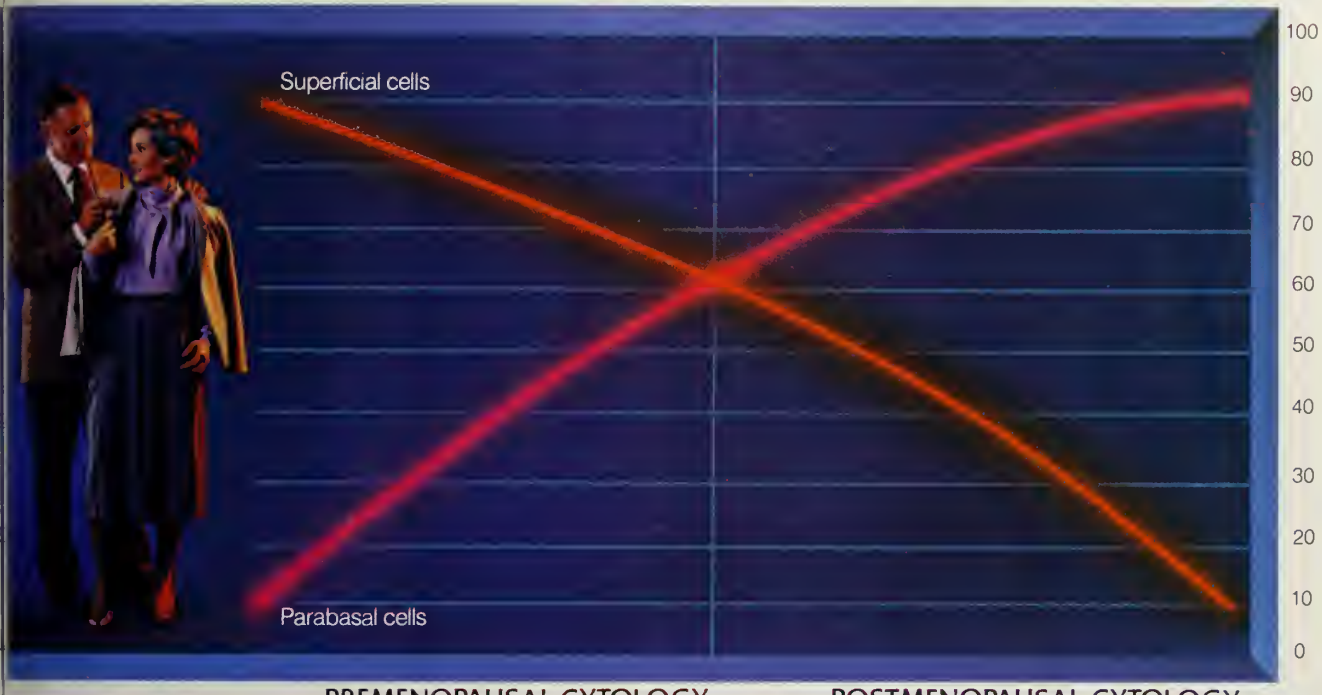
FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories

THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

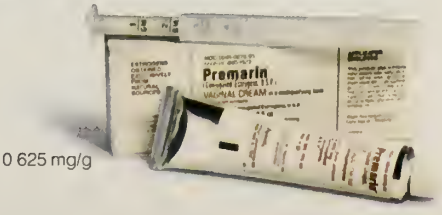
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

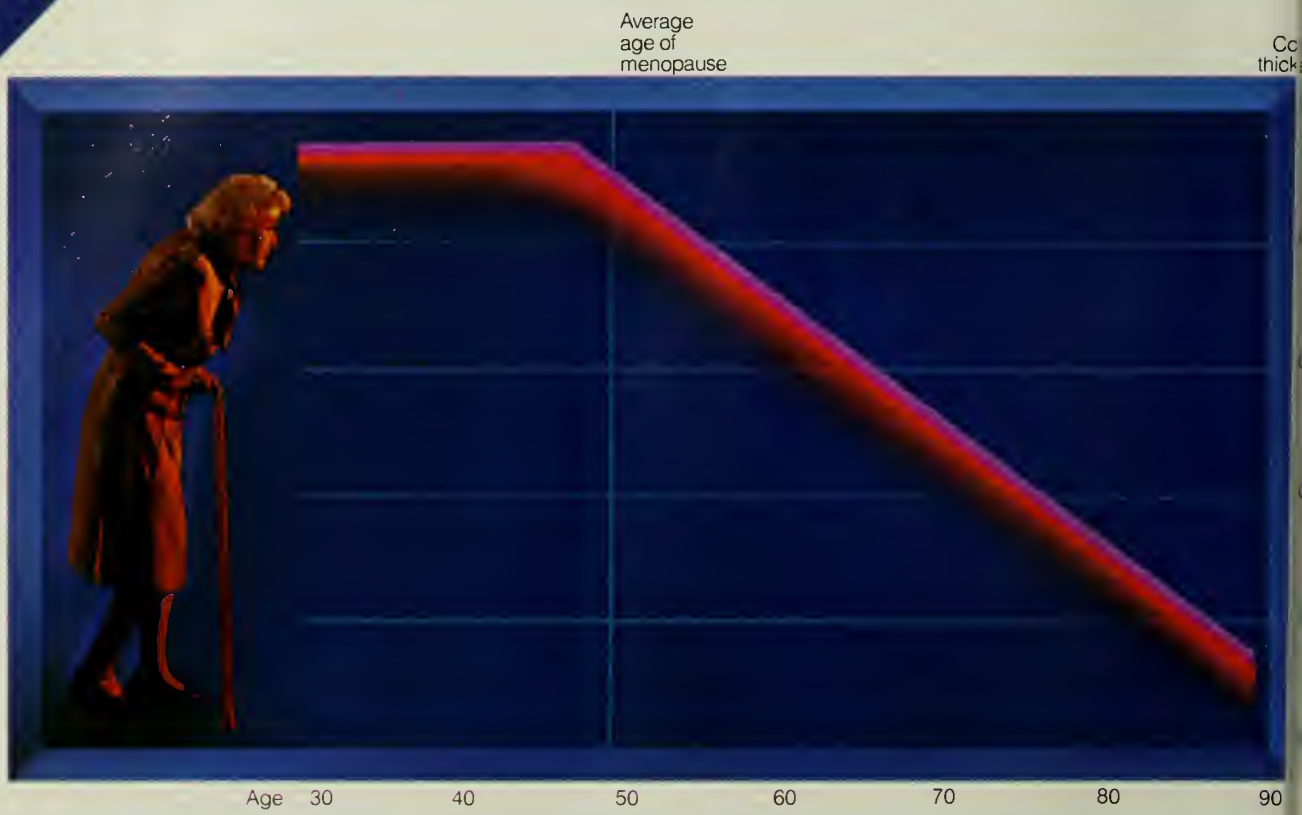
FOR ATROPHIC VAGINITIS

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis.

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema, changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.), No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **8934/984**

REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al. Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al. Estrogen replacement therapy: Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull*, June 1983, pp 1-5. 4. Ayers LJ. The maturation index. A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G. Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ. Age, estrogen, and bone density. *Clin Obstet Gynecol* 1981;24:203-218. 7. Gordan GS, Picchi J, Roof BS, et al: Postmenopausal osteoporosis. *Am Fam Physician* 1973;8:74-83. 8. US Bureau of the Census. *Statistical Abstract of the United States* 1982-83, ed. 103. Washington, DC, US Dept of Commerce, 1982, p 25. 9. Mallette LE: Osteoporosis. Approaching treatment with optimism. *Postgrad Med* 1982;72:271-278.

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There is a Name for Outstanding Leadership in Quality Psychiatric Care. Charter Medical Corporation.

And Here's Where That Leadership Stands Out in the West.

For many patients, the most effective treatment can be best delivered by psychiatrists, working with highly qualified professionals, in a free-standing hospital whose entire staff is dedicated to quality psychiatric care.

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You can depend on the fact that the staff will work with you to design and implement an individualized treatment plan for your patient. Involvement of the patient's family in the treatment process will be encouraged. There will be regular communication, between the hospital and the referring professional, about the patient's status. All psychiatrists on staff are Board Certified or Board Eligible. There is a wide variety of therapies available to enhance individualized treatment. And every Charter Medical Hospital has been designed to provide a modern therapeutic environment to promote your patient's recovery.

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6060 Paramount Blvd.
Long Beach, California 90805
(213) 634-9102

Beds: 227
Psychiatric Staff: 59
Programs: Adult, Adolescent and Child Psychiatric

Other Programs: Christian Psychiatric Unit; 24 Hour Crisis Intervention Service; Psychiatric Emergency Team

For further information about Charter Baywood or admission procedures, contact:

Acting Medical Director:
Leon Marder, M.D.
Hospital Administrator: Diana Goulet

Charter Grove Hospital

2005 Kellogg Drive
Corona, California 91720
(714) 735-2910

Beds: 86
Psychiatric Staff: 15
Programs: Adult and Adolescent Psychiatric; Adult Addictive Disease.

Other Programs: Women's Program; Eating Disorders; and Christian Psychiatric

For further information about Charter Grove or admission procedures, contact:

Medical Director: William Cohen, M.D.
Hospital Administrator: Jim Fridlington

Charter Oak Hospital

1161 East Covina Blvd.
Covina, California 91724
(213) 966-1632

Beds: 74
Psychiatric Staff: 14
Programs: Adult, Adolescent and Child Psychiatric; Adult Addictive Disease

Other Programs: Premenstrual Syndrome Clinic

For further information about Charter Oak or admission procedures, contact:

President of Medical Staff:
Adib Bitar, M.D.
Hospital Administrator: Jim Sholes

Charter Pacific Hospital

4025 West 226th St.
Torrance, California 90505
(213) 373-7733

Beds: 96
Psychiatric Staff: 36
Programs: Adolescent, Child and Young Adult Psychiatric; Adult and Adolescent Addictive Disease

Other Programs: Pediatric Neuro/developmental Diagnostic Unit; Charter Clinic, in Santa Ana, offers Neuropsychological child and adolescent services.

For further information about Charter Pacific or admission procedures, contact:

Director of Adolescent Unit:
Michael J. Levine,
Hospital Administrator: Jim Hackett

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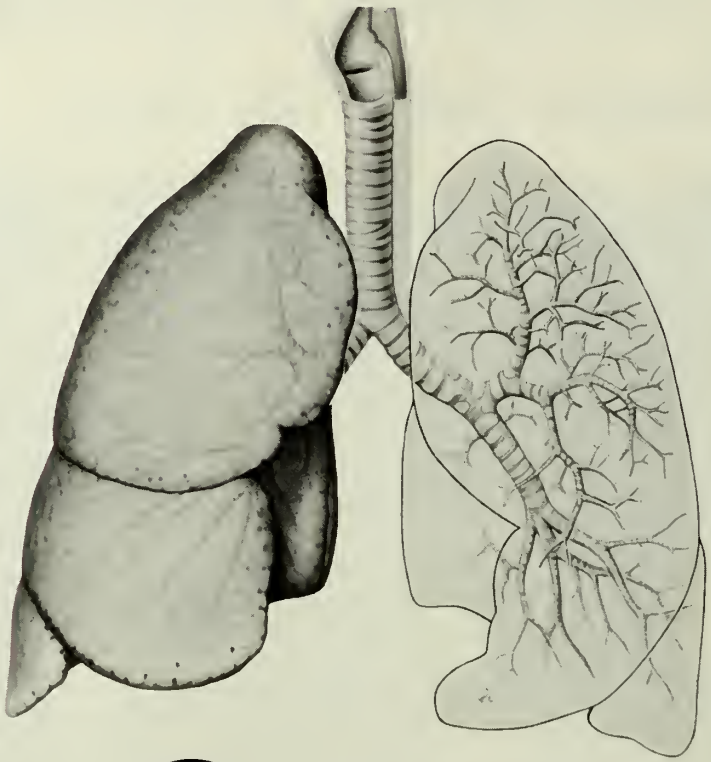
Consider the causative organisms...



Ceclor®
cefaclor
250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, *H. influenzae*, *S. pneumoniae*, *S. pyogenes*
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary Consult the package literature for prescribing information

Indications and Usage Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile* Other causes of colitis should be ruled out

Precautions *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly) There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

Note Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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Additional information available to the profession on request from Eli Lilly and Company Indianapolis, Indiana 46285

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BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM (diltiazem HCl)
balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

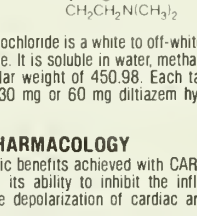
2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-8enzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina· CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1 **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).

2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and AOVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CAROIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CAROIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CAROIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. 8ecause many drugs are excreted in human milk, exercise caution when CAROIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CAROIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CAROIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3% asthenia (1.2%), AV block (1.1%). In addition, the following event were reported infrequently (less than 1%) with the order of presenta tion corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradyca dia, palpitations, congestive heart failure syncope.
Nervous System:	Paresthesia, nervousness, somnolence tremor, insomnia, hallucinations, and amnesi
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomitin mild elevations of alkaline phosphatase, SGO SGPT, and LOH.
Oermatologic:	Pruritus, petechiae, urticaria, photosensitivit
Other·	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes o vasospastic angina developed periods of transient asymptomati asystole approximately five hours after receiving a single 60-m dose of CAROIZEM.

The following postmarketing events have been reported infr quently in patients receiving CAROIZEM: erythema multiforme; le kopenia; and extreme elevations of alkaline phosphatase, SGO SGPT, LOH, and CPK. However, a definitive cause and effect betwee these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limite Single oral doses of 300 mg of CAROIZEM have been well tolerate by healthy volunteers. In the event of overdosage or exaggerate response, appropriate supportive measures should be employed addition to gastric lavage. The following measures may be considere

8radycardia	Administer atropine (0.60 to 1.0 mg). If the is no response to vagal blockade, administ isoproterenol cautiously.
High-Oegree AV 8lock	Treat as for bradycardia above. Fixed high degree AV block should be treated with ca diac pacing.
Cardiac Failure	Administer inotropic agents (isoproteren dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarteren bitartrate).

Actual treatment and dosage should depend on the severity of t clinical situation and the judgment and experience of the treatir physician.

The oral/LO_{50}'s in mice and rats range from 415 to 740 mg/k and from 560 to 810 mg/kg, respectively. The intravenous LO_{50}'s these species were 60 and 38 mg/kg, respectively. The oral LD_{50} dogs is considered to be in excess of 50 mg/kg, while lethality wa seen in monkeys at 360 mg/kg. The toxic dose in man is not know but blood levels in excess of 800 ng/ml have not been associate with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Cor nary Artery Disease or Angina Pectoris at Rest Due to Cor nary Artery Spasm. Dosage must be adjusted to each patient needs. Starting with 30 mg four times daily, before meals and bedtime, dosage should be increased gradually (given in divid doses three or four times daily) at one- to two-day intervals un optimum response is obtained. Although individual patients m respond to any dosage level, the average optimum dosage ran appears to be 180 to 240 mg/day. There are no available data concer ing dosage requirements in patients with impaired renal or hepat function. If the drug must be used in such patients, titration should carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acu anginal attacks during CAROIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CAROIZEM may be safe coadministered with short- and long-acting nitrates, but the have been no controlled studies to evaluate the antiangir effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NI 0088-1771-47) and in Unit Dose Identification Paks of 100 (NI 0088-1771-49). Each green tablet is engraved with MARION on o side and 1771 engraved on the other. CARDIZEM 60-mg scor tablets are supplied in bottles of 100 (NOC 0088-1772-47) and in U Oose Identification Paks of 100 (NOC 0088-1772-49). Each yell tablet is engraved with MARION on one side and 1772 on the oth

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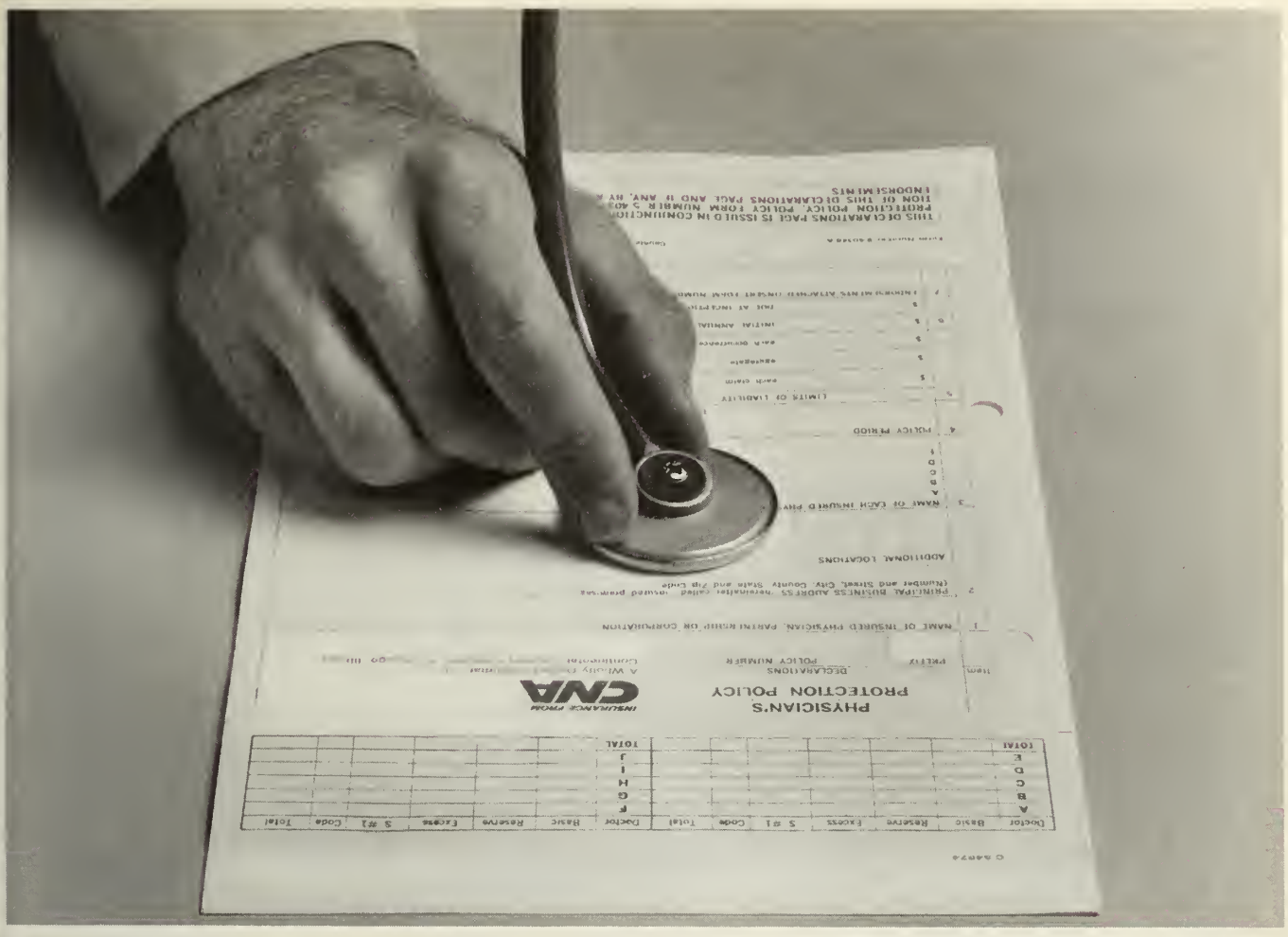

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Dr Johnson is in private practice in Boise, Idaho.

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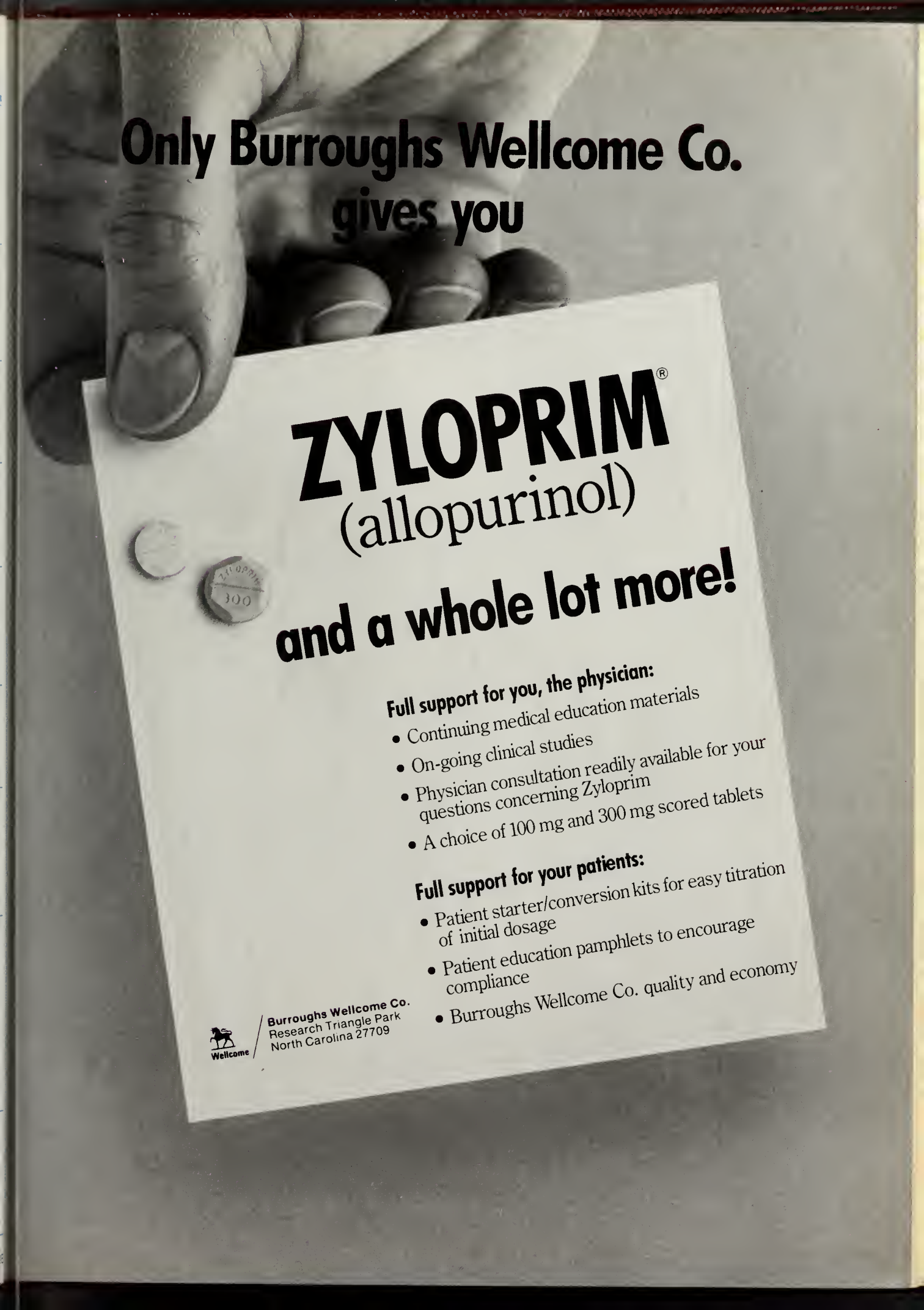
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In active duodenal ulcer

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

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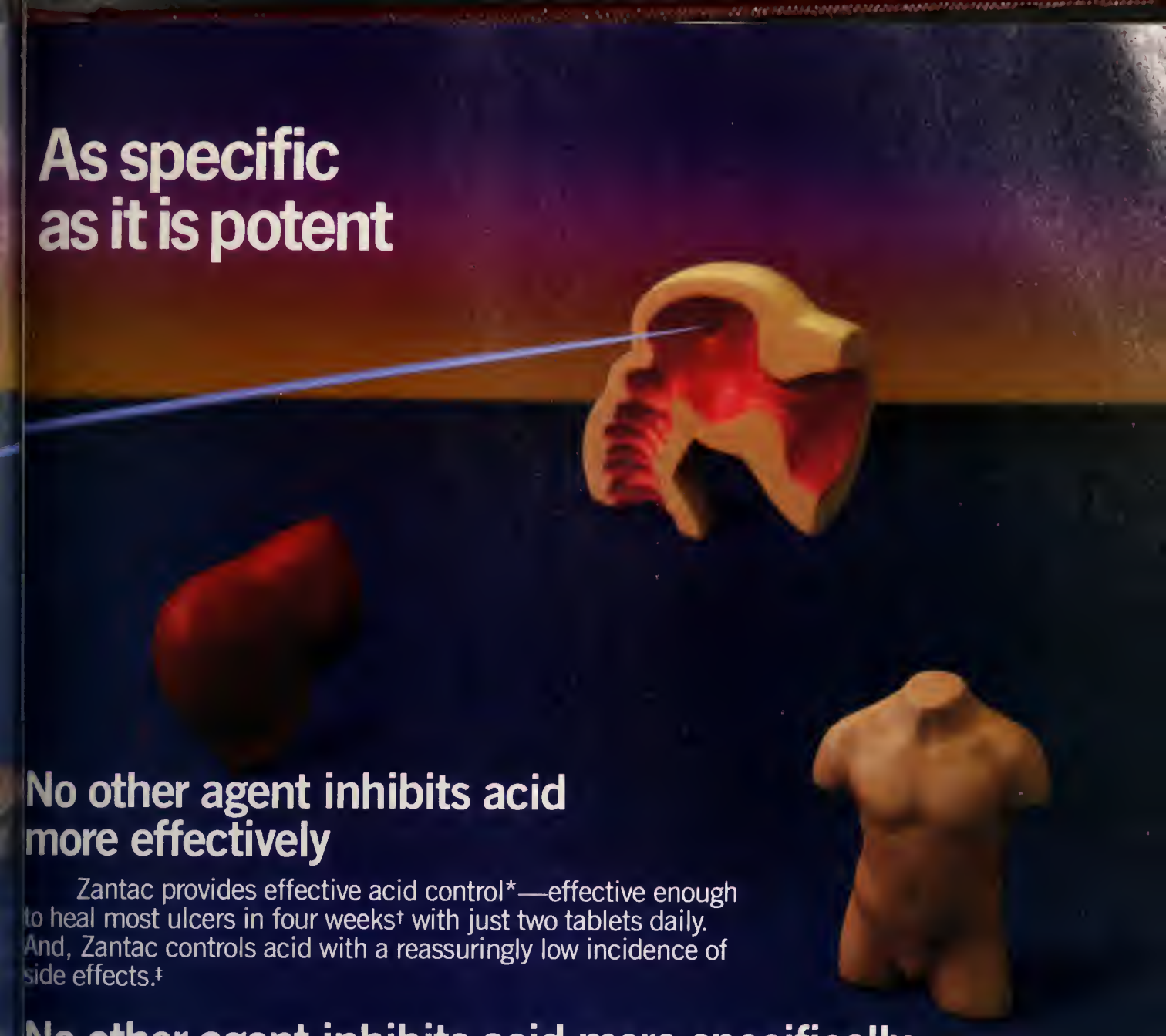
As specific as it is potent



No other agent inhibits acid more effectively

Zantac provides effective acid control*—effective enough to heal most ulcers in four weeks† with just two tablets daily. And, Zantac controls acid with a reassuringly low incidence of side effects.‡

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Zantac is highly selective in action—it does not interfere with androgen or gonadotropin levels:

- No effect on count, motility or morphology of sperm
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In addition, Zantac does not significantly interfere with the hepatic metabolism of commonly used drugs. Unlike cimetidine, Zantac may be administered concomitantly with theophylline, warfarin, propranolol or phenytoin, without significant alteration of their serum levels.

No other agent inhibits acid more conveniently

The convenient b.i.d. dosage not only encourages compliance, but through 24-hour acid control, also provides a reduction in both daytime and nocturnal pain. And, Zantac may be taken with food.

*It is not known exactly how much inhibition of gastric acid secretion is required to heal ulcers.
†80% of patients can be expected to show complete healing at the end of two weeks; if healing is documented, treatment can be discontinued.
‡See ADVERSE REACTIONS section of Brief Summary for complete description of reported events.

Please see following page for Brief Summary.

In active duodenal ulcer

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

The selective inhibitor

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: ZANTAC® (ranitidine hydrochloride) is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.

2. The treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy. **2.** Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests: False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, E Coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy: ***Pregnancy Category B.*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC® (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC.® The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Rare cases of reversible mental confusion, agitation, depression and hallucinations have been reported, predominantly in severely ill elderly patients.

Cardiovascular: Rare reports of tachycardia, bradycardia, premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 q.i.d. IV for 5 days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia and pancytopenia.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC, no anti-androgenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC® (ranitidine hydrochloride) was substituted. However, occasional cases of gynecomastia, impotence and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumental: Rash and rarely alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), small increases in serum creatinine.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in dogs receiving doses of ZANTAC® in excess of 225 mg/kg/day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC,® the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening.

Revised: July 1984

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ALLERGY AND IMMUNOLOGY

October 20—**Allergy Update—A Clinical Symposium.** Allergy Foundation of Northern California, Allergy Association of Northern California and the California Society of Allergy at Holiday Inn Union Square, San Francisco. Saturday. Contact: Dr Chester Trossman, 500 E. Remington Dr., Sunnyvale 94087. (408) 730-0812.

October 24-28—**American Association for Clinical Immunology and Allergy Meeting** at San Diego. Wednesday-Sunday. Contact: Howard S. Silber, Exec. Dir., PO Box 912-DTS, Omaha, NE 68101. (402) 551-0801.

October 25-28—**Allergy, Immunology and Infectious Disease.** Symposium Maui, Inc. and Hawaii Chapter American Academy of Family Physicians at Maui Marriott, Kaanapali, Maui. Thursday-Sunday. 18 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., PO Box10185, Lahaina, Maui, HI 96761. (808) 661-8032.

December 27-29—**Allergy and Asthma.** Hawaii Medical Association and Hawaii AAFP at Royal Lahaina Resort, Maui. Thursday-Saturday. $275. 13.5 hrs. Contact: Joe Harrison, MD, Dir., PO Box 10185, Lahaina, Maui 96761.

January 3-5—**Allergy and Dermatology.** Symposium Maui, Hawaii Medical Association, and Hawaii American Acadaemy of Family Practice at Royal Lahaina Resort, Maui. Thursday-Saturday. 13.5 hrs. $275. Contact: Symposium Maui, Joe Harrison, MD, Director, PO Box 10185, Lahaina, Maui 96761.

January 10-12—**Allergy and Immune Diseases in Children.** Symposium Maui, Hawaii Medical Association and Hawaii American Academy of Family Practice at Royal Lahaina Resort, Maui. Thursday-Saturday. 13.5 hrs. $275. Contact: Symposium Maui, Joe Harrison, MD, Director, PO Box 10185, Lahaina, Maui 96761.

ANESTHESIOLOGY

October 20—**Annual Anesthesiology Symposium.** Kaiser Permanente Southern California Medical Group at Sheraton Premiere Hotel, Universal City. Saturday. Contact: Department of Clinical Services, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation and Childrens Hospital of Los Angeles at Los Angeles. Friday-Sunday. Contact: Wayne Herbert, MD, Program Dir., Ped. Anes. Fndn, PO Box 54700, Los Angeles 90054. (213) 669-2262.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

(Continued on Page 461)

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First-step blood pressure control with optimal simplicity

Benefits diuretics cannot offer... Once-daily INDERAL LA (propranolol hydrochloride) with its smooth 24-hour control of blood pressure provides a high degree of patient acceptance without potassium problems, plus the cardiovascular benefits of the world's leading beta blocker.

Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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(PROPRANOLOL HCl) LONG ACTING CAPSULES

Just once each day for initial therapy in hypertension.

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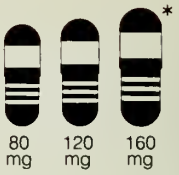


BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length and diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the platelets and in the cerebral blood vessels.

Beta receptor blockade can be useful in conditions in which beclouding of cathecholamine functional changes, sympathetic activity is detrimental to the patient. Further, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

Just once each day for initial therapy in HYPERTENSION.

(Continued from Page 457)

CANCER

October 18-20—**8th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. $300. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

December 7-9—**2nd Annual Recent Advances in Occupational Cancer Focus on Prevention.** UCSF at Golden Gateway Holiday Inn. San Francisco. Friday-Saturday. $150.

December 12—**19th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. Contact: Linda Morgado, Med. Staff Coord., N. T. Enloe Memorial Hospital, W. 5th Ave. and The Esplanade, Chico 94926. (916) 891-7300.

CARDIOLOGY

October 19-21—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center and Medical Education Resources at Islandia Hyatt, San Diego. Friday-Sunday. 13 hrs. Contact: Med. Ed. Resources, 5808 So. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

October 26,28—**ECG Interpretation, Arrhythmia Management, and Cardiac Rehabilitation.** International Medical Education Corporation at San Francisco. Friday-Sunday. 13 hrs. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 1-3—**7th Annual Fall Symposium on Cardiovascular Update, Behavioral Sciences and New Trends in Medicine.** South Bay Hospital at Hotel Del Coronado, Coronado. Thursday-Saturday. 14 hrs. $235. Contact : Cheryl Farmer, Coord. Med. Ed., South Bay Hospital, 514 N. Prospect Ave., Redondo Beach 90277. (213) 318-4668.

November 2-4—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center and Medical Education Resources, 5808 So. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

November 2-4—**The Diagnosis and Management of the Acute Myocardial Infarction.** International Medical Education Corporation at Newporter Inn, Newport Beach. Friday-Sunday. Contact: Beverly Jacobsen. (800) 525-8651.

November 9-10—**Cardiology Update 1984.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. Contact: Lore Kahane, C-SMC, PO Box 4870, Los Angeles 90048. (213) 855-5547.

November 10—**Update in Pulmonary Medicine for the Primary Care Physician.** University of San Francisco, Fresno Extension. Saturday. 6 hrs. $80. Contact: Sharon Balestra, Program Rep., UC Med Ed Program CSJV/EPME, 2615 E. Clinton Ave., Fresno 93703. (209) 225-6100, x 562 or 207.

November 30-December 2—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress & Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 30-December 2—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact : Beverly Jacobsen, 64 Inverness Dr. E., Englewood, CO 89112. (800) 525-8651.

December 7-9—**Cardiovascular Disease: Non-Invasive Diagnostic Method (Stress and Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at San Diego. 13 hrs. Friday-Sunday. Contact: IMEC, 64 Inverness Drive E., Englewood, CO 80112. (800) 525-8651.

December 7-9—**Advances in Heart Disease 1984.** American College of Cardiology at Hyatt Regency Hotel, San Francisco. Contact: ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

January 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado Health Sciences Center at MGM Grand Hotel, Las Vegas. Friday-Sunday. 13 hrs. Contact: Med. Ed. Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

EMERGENCY MEDICINE

October 29-30—**Advanced Cardiac Life Support.** Emergency Care Education Center Inc., Emergency Department Physicians Inc., and Greater Los Angeles Affiliate American Heart Association at Queen Mary, Long Beach. Monday-Tuesday. 16 hrs. $225. Contact: ECEC-ACLS, 4640 Admiralty Way, Ste. 508, Marina del Rey 90291. (213) 822-1312.

October 29-November 2—**Intensive Care.** STAN at Rickey's Hyatt, Palo Alto. Monday-Friday.

October 31-November 2—**EMS Today.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 19 hrs.

November 12-16—**Postgraduate Institute for E.R. Physicians, Symposium III.** UCSD at Holiday Inn Embarcadero, San Diego. Monday-Friday.

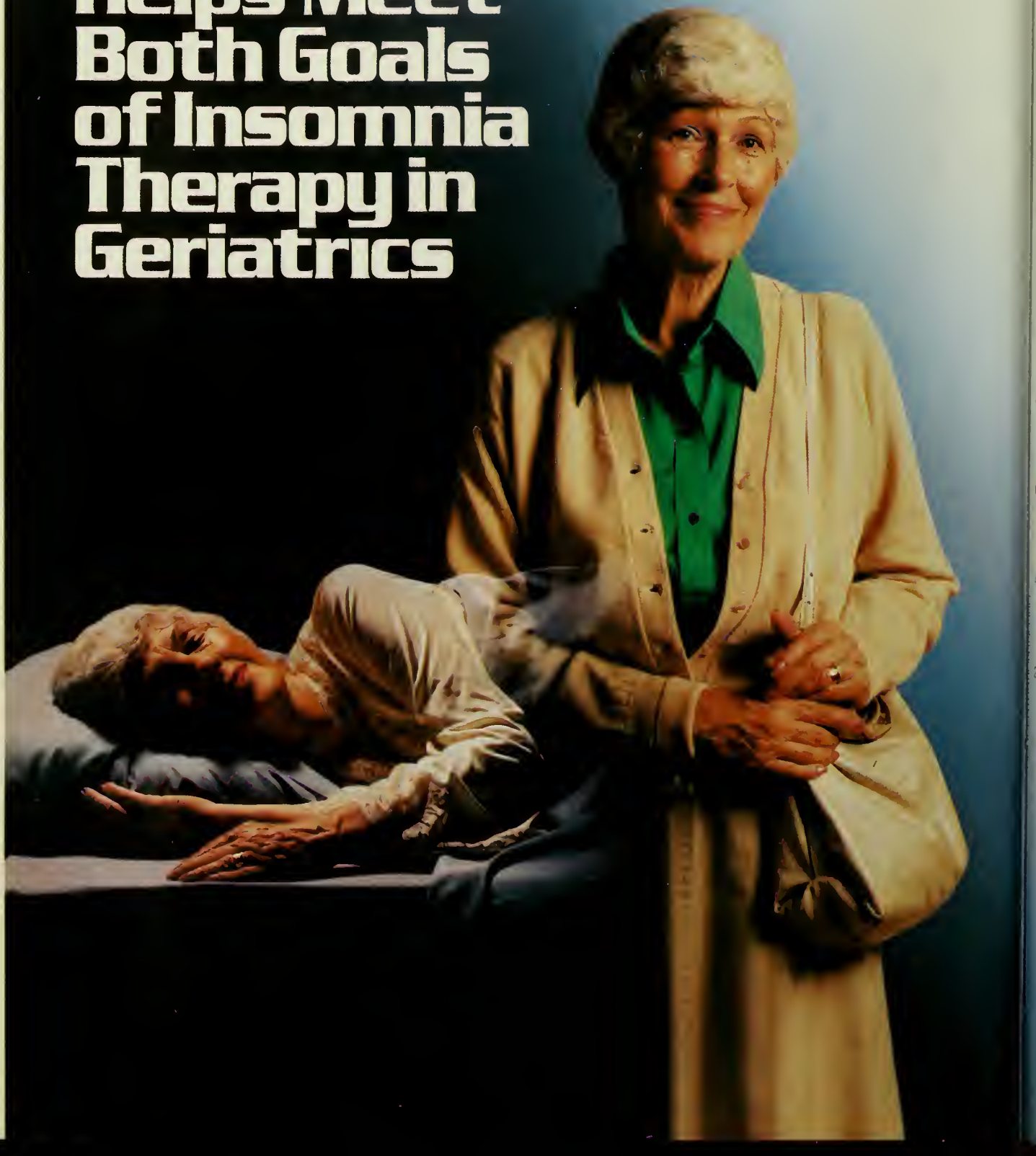
December 2-7—**Kauai 1984 "Current Concepts in Emergency Care."** The Institute for Emergency Medical Education and the Washington Chapter of the American College of Emergency Physicians at Kauai Surf Hotel, Kauai. Sunday-Friday. 25 hrs. Contact:

(Continued on Page 465)

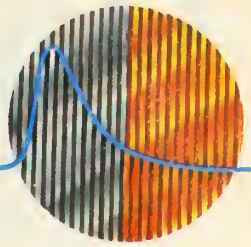
Halcion® 0.25 mg Tablets

triazolam C IV

Helps Meet Both Goals of Insomnia Therapy in Geriatrics



Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

© 1983 The Upjohn Company

Halcion Tablets
triazolam (IV)

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervisic

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1

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CONTINUING MEDICAL EDUCATION

(Continued from Page 461)

Georgine Fleck, Kailani World Travel, 4192 Meridian Avenue, Bellingham, WA 98277-9951. (800) 426-2561.

December 10-14—**Postgraduate Institute for E.R. Physicians, Symposium II.** UCSD at La Jolla Village Inn, La Jolla. Monday-Friday. (619) 452-3940.

INTERNAL MEDICINE

October 17—**Diabetes—1984.** The Hospital of the Good Samaritan at Hyatt Regency Hotel Los Angeles, Los Angeles. Wednesday. Contact: Dolores Gay, Coordinator of Symposia, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

October 19-21—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Practicing Physician.** Continuing Medical Education Associates at Vacation Village Hotel, San Diego. Friday-Sunday. Contact: Jackie Shiller, PO Box 84296, San Diego, CA 92138. (619) 223-2997.

October 24—**14th Annual Respiratory Medicine Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. Contact: Linda Morgado, Med. Staff Coord., N. T. Enloe Memorial Hospital, W. 5th Ave. and The Esplanade, Chico 94926. (916) 891-7300.

November 2-3—**Thyroid/Diabetes Workshop.** UCSF. Friday-Saturday.

November 2-4—**Practical Endocrinology: Workshop in Thyroid and Diabetes.** UCSF at Claremont Resort Hotel, Berkeley. Friday-Sunday. Reg. Info.: 666-5808. Program Info.: 666-4251.

November 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. $200. Contact: UCI. (714) 634-6868.

November 10—**Infectious Disease.** UCD at Holiday Inn Holidome, Sacramento. Saturday.

November 10—**Pulmonary Medicine.** UCSF at Fresno. Saturday. Contact: Sharon Balestra (209) 225-6100 Ext. 562 or 207.

November 14—**13th Annual Gastroenterology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. Contact: Linda Morgado, Med. Staff Coord., N. T. Enloe Memorial Hospital, W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7300.

November 14—**Rheumatology—X-Ray of the Joints.** LLU. Wednesday.

November 16-18—**Pulmonary Medicine and Office Spirometry for P.C. Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday.

(Continued on Page 554)

It Pays to Save Potassium
K+
Potassium-Sparing
DYAZIDE®
Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.
In Hypertension*, When You Need to Conserve K+
Serum K+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

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Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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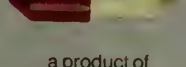

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Clinical Investigation

Duration of Type I Diabetes Affects Glucagon and Glucose Responses to Insulin-Induced Hypoglycemia

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The glucagon response to hypoglycemia, which fulfills a primary role toward restoring the plasma glucose level, is blunted or absent in most patients with type I diabetes. To identify predictive factors for this abnormality and for the capability of glycemic counterregulation, we investigated the relationship between the duration of diabetes and glucagon and glucose responses to insulin-induced hypoglycemia. In 18 type I diabetic patients with 1 through 28 years of disease who had no detectable autonomic neuropathy, individual glucagon increments after insulin hypoglycemia were inversely correlated with the duration of disease ($r = -.53$, $P < .025$). Patients with disease for ten or fewer years showed a glucagon rise that was lower than in controls but significantly higher than in patients with a duration of more than ten years. The plasma glucose rise after the nadir correlated with peak glucagon increments ($r = .60$, $P < .01$); eight of the nine patients with glycemic increments comparable to normals had had diabetes for ten years or less. Thus, having diabetes for more than ten years implied that not only were glucagon responses to insulin hypoglycemia severely compromised but also that the abrupt restoration of plasma glucose levels was impaired. These findings should be taken into account when establishing goals and modalities for tight metabolic control.

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The availability of new technology and growing evidence that sustained near-normoglycemia corrects in diabetic patients functional abnormalities that may represent prodromes of the classic complications[1-4] are encouraging the achievement of tight metabolic control of diabetes. Intensive insulin therapy has its complications, however, the most serious of which is the increased risk of profound hypoglycemia.[5] It would thus be valuable to isolate clinical characteristics capable of prospectively identifying patients at increased risk of this complication.

Under normal circumstances a decline in the plasma glucose level is briskly corrected by accelerated hepatic glycogenolysis driven by the increased secretion of epinephrine and glucagon.[6] Glucagon has been attributed a primary role in the recovery from hypoglycemia because, in the absence of its response, even exaggerated increments in epinephrine fail to restore plasma glucose to normal levels.[6,7]

Although patients with type I diabetes manifest, as a group, a blunted or absent glucagon response to hypoglycemia and compromised glycemic counterregulation,[7-10] individual patients may have adequate responses. The recent report by Bolli and co-workers[11] of a striking inverse correlation between the duration of type I diabetes and glucagon responses to hypoglycemia suggests that the duration of diabetes may be a useful clinical predictor of disturbances in glycemic counterregulation. In other studies, however, diabetic patients with clinical or experimental evidence of defective counterregulation could not be separated from those

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manifesting adequate responses on the basis of glucagon behavior nor of the duration of diabetes.[12,13]

We have thus sought to reexamine to what extent the duration of type I diabetes and attending glucagon responses to hypoglycemia can be useful in predicting the capability of restoring plasma glueose levels.

Patients and Methods

Studies were approved by the Committee on Human Research of the University of California at San Francisco and an informed written consent was obtained from all participating persons. The clinical characteristics of the 18 patients with diabetes are summarized in Table 1. They were all ketosis-prone and insulin-dependent. At the time of study patients were, with the noted exception, all within ideal body weight, free from proliferative retinopathy, advanced kidney disease (serum creatinine levels were less than 1.3 mg per dl) and other vascular complieations, none had resting tachycardia (more than 90 beats per minute) nor postural hypotension (a fall in systolic pressure of 30 mm of mercury or more). Control subjects were matched for age and sex and all were within ideal body weight. The only medication was insulin for the diabetic patients, all of whom were on twice-a-day injections of regular mixed with an intermediate-acting insulin preparation (NPH or Lente). Because we had elected to study patients under circumstances that would mimic their daily control, tests were done after an overnight admission to the General Clinical Researeh Center while the patients were receiving their usual insulin therapy. Insulin-tolerance tests were administered after an overnight fast, starting at 0800 hours, the diabetic patients having received their last insulin dose no later than 2000 hours the previous night. In all subjects an antecubital intravenous line was established and kept patent with an infusion of 0.9% saline solution and, after a 30-minute equilibration period, baseline blood speeimens were obtained at 20- to 30-minute intervals. The insulin dose for diabetic patients was decided on the basis of three baseline glucose values: depending on actual levels and direction and rate of ehanges, we administered between 0.12 and 0.2 units per kg of body weight for fasting glucose levels of less than 150 mg per dl and between 0.2 and 0.5 units per kg for glucose levels greater than 150 mg per dl. Normal controls received 0.15 units per kg. To all subjects insulin was given as a bolus at zero time, with the exception of patients 2, 5, 6 and 9, who received the 0.4 to 0.5 units per kg dose. In these patients half of the insulin dose was given at zero time and half at 45 to 60 minutes, depending on the rate of deeline of plasma glueose. Blood specimens were obtained every 15 minutes after the insulin injection; in six of the eight control subjects specimens were also obtained at 3, 6, 9 and 12 minutes after insulin injection to determine the extent of glueagon suppression.

In all specimens we measured plasma glueose,[14(p1)] pancreatic glucagon (antiserum 30K,[15] cortisol[16] and serum growth hormone levels.[17] Tests were considered valid for inclusion in the study when at least one plasma glucose value was below 40 mg per dl. The slope of the line connecting glucose values between zero time and the nadir was taken to describe the rate of glucose fall; on that, the half-life and the rate of disappearanee (K) were calculated. Hormone increments were computed in individual subjeets as the differenee between the peak value after glucose nadir and the mean baseline value (–30 and 0 minutes); glucagon suppression was determined as the difference between the mean baseline value and the lowest level observed before the glucose nadir. The glycemie increment after hypoglyeemia was eomputed in two ways: as the difference between the value recorded 15 minutes after the nadir and the nadir itself; and as the area under the curve described by the increments at 15 and 30 minutes postnadir, the value at the nadir having been assigned a value of zero.

Although no multisystemic testing for autonomic dysfunetion was done, we had obtained in all patients a pulse rate in the basal state and during the performance of the insulin-tol-

TABLE 1.—*Clinical and Experimental Data on Patients With Diabetes*

Patient, Sex	*Age Years*	*Duration of Diabetes Mellitus Years*	*Baseline Values*		*Insulin Given units (per kg)*	*Plasma Glucagon Suppression pg/ml*	*Plasma Glucagon Increment in ITT pg/ml*
			Glucose mg/dl	*Glucagon pg/ml*			
1* ♂	30	28	134	50	12.0 (0.15)	27	33
2† ♂	27	22	156	140	30.0 (0.4)	47	20
3 ♂	28	18	130	37	11.0 (0.15)	19	20
4‡ ♀	20	17	111	33	12.0 (0.2)	22	78
5 ♂	26	14	175	30	36.0 (0.4)	13	23
6 ♀	42	14	288	145	34.0 (0.5)	100	0
7 ♂	25	10	60	10	9.0 (0.15)	0	70
8 ♂	25	10	109	88	15.0 (0.2)	31	102
9 ♂	22	8	250	57	38.0 (0.5)	27	110
10 ♂	20	8	89	70	10.0 (0.15)	0	108
11 ♂	27	7	185	44	25.0 (0.3)	84	90
12 ♂	25	5	104	22	10.0 (0.15)	16	39
13 ♂	28	5	229	77	21.0 (0.25)	60	189
14 ♂	19	4	88	56	9.6 (0.15)	8	55
15 ♂	23	4	73	11	8.2 (0.12)	12	36
16 ♂	28	2	120	110	9.0 (0.15)	32	300
17 ♂	20	2	167	118	18.0 (0.24)	27	90
18 ♂	18	1	132	97	15.0 (0.2)	64	103

ITT = insulin tolerance test

*Patient also has impotence.

†Sensory neuropathy and 2+ proteinuria are also present.

‡The patient weighs 20% more than ideal body weight.

erance test, as well as supine and standing blood pressures. In patients 2, 3 and 6, who showed the least of all glucagon responses to hypoglycemia, we did a Valsalva's maneuver, a reliable and reproducible test of autonomic nerve function.[18] The results are expressed as the "Valsalva ratio," which is the longest RR interval after the maneuver (reflecting the overshoot bradycardia) to the shortest interval during the maneuver (reflecting the tachycardia during strain).

Group data are expressed as the mean ± standard deviation. The two groups were compared using the Student's *t* test (nonpaired analysis). When more than two groups were compared, statistical analysis was done by analysis of variance, followed by multiple-range testing (Duncan's). Least-squares regression was used for line fitting.

Results

Glucagon Response to Insulin-Induced Hypoglycemia and Duration of Diabetes

In normal subjects plasma glucose nadirs (28 ± 5 mg per dl) occurred between 15 and 30 minutes after the injection of insulin and the peak glucagon increment (184 ± 71 pg per ml) was noted between 30 and 45 minutes. In diabetic patients plasma glucose nadirs (30 ± 9 mg per dl) were reached between 30 and 120 minutes after giving insulin, depending on the initial plasma glucose values (reported in Table 1). The basal plasma glucagon level (66 ± 42 pg per ml) was not different from that of normal subjects (66 ± 40), but a wide spectrum of responses to hypoglycemia was observed: as shown in Table 1, increments ranged from 300 pg per ml to undetectable. A significant inverse correlation was found (Figure 1) between duration of diabetes and glucagon responses to hypoglycemia ($r = -.53$, $P < .025$).

Because no normal glucagon responses were noted in patients with diabetes for more than ten years, we compared their glucagon increments with those in controls and in patients who had had diabetes for ten years or less (Table 2). The group of patients who had had diabetes for more than ten years had a glucagon rise of 29 ± 26 pg per ml, significantly lower than that of controls ($P < .005$) and patients with 10 or fewer years of disease ($P < .025$). The difference with the latter group occurred despite the fact that none of the experimental variables that may have positively or negatively affected the glucagon response (basal glucose, glucose nadir, absolute glucose decline, insulin administered, rate of glucose decline, glucagon suppression) were significantly different between the two groups.

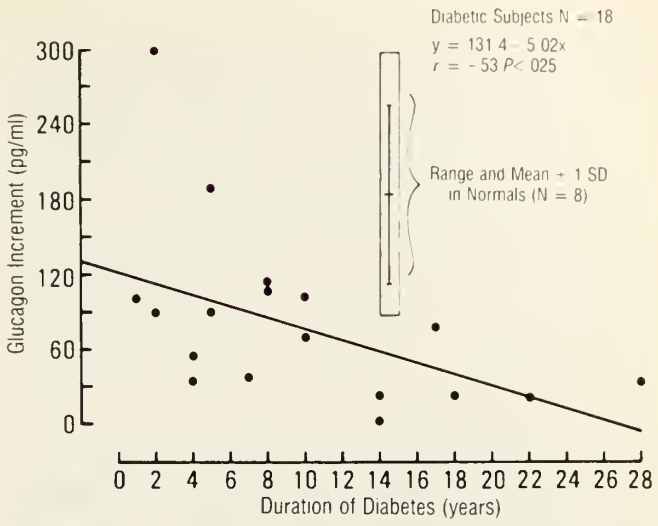
Diabetic Subjects N = 18
y = 131.4 − 5.02x
r = −.53 P< .025
Range and Mean ± 1 SD in Normals (N = 8)
Glucagon Increment (pg/ml)
300
240
180
120
60
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Duration of Diabetes (years)

Figure 1.—Correlation between duration of type I diabetes and peak increments of plasma glucagon level after insulin hypoglycemia. SD = standard deviation.

Patients with ten or fewer years of diabetes also showed, as a group, a lesser glucagon response to hypoglycemia than controls (107 ± 71 pg per ml versus 184 ± 71 in controls, $P < .05$). The only other variable that differed statistically between the two groups was the rate of glucose fall (3.6 ± 1.6 mg per dl a minute versus 5.2 ± 1.7 in controls, $P < .05$). Of interest, however, is that no significant correlation was found between the individual rate of glucose disappearance and glucagon increment after hypoglycemia in either group. In addition, in diabetic patients there was no correlation between basal glucose levels, insulin administered, glucagon suppression and glucagon increments after hypoglycemia.

Glucagon Responses to Hypoglycemia and Restoration of Plasma Glucose

In normal subjects, 15 minutes after the observed nadir, plasma glucose levels had increased by 15 ± 6 mg per dl and the range of increments was 5 to 27 mg per dl. Among the 12 patients with ten or fewer years of disease, a glycemic response within the range of normal was displayed by 8 (66%), whereas among the 6 patients with diabetes for a longer duration, the glycemic response of only 1 (16%) fell within the control range. Overall, a positive correlation was evident (Figure 2) between increments in glucagon and in-

TABLE 2.—*Comparison of Group Data for Metabolic Variables and Glucagon Responses to Hypoglycemia*

	Normal Subjects N = 8 Mean ± SD	*Patients With ≤ 10 Years of DM N = 12 Mean ± SD*	*Patients With > 10 Years of DM N = 6 Mean ± SD*
Basal glucose, mg/dl	86 ± 8	133 ± 61	165 ± 63*
Insulin given, units/kg	0.15 ± 0.00	0.21 ± 0.10	0.3 ± 0.15
Plasma glucose nadir, mg/dl	28 ± 5	30 ± 9	30 ± 9
Absolute plasma glucose decline, mg/dl	57 ± 9	101 ± 53	131 ± 66*
Rate of plasma glucose decline (K), mg/dl/min	5.2 ± 1.7	3.6 ± 1.6*	3.0 ± 0.6*
Plasma glucagon suppression, pg/ml	13 ± 11	30 ± 26	38 ± 32
Plasma glucagon increment, pg/ml	184 ± 71	107 ± 71*	29 ± 26†‡

DM = diabetes mellitus, SD = standard deviation

*$P < .05$ versus controls. †$P < .005$ versus controls. ‡$P < .025$ versus DM ≤ 10 years.

crements in plasma glucose 15 minutes postnadir ($r = .60$, $P < .01$). Similar results were obtained when the correlation was sought between the increments in glucagon and the areas under the curve for the plasma glucose rise during the 30 minutes following the nadir ($r = .56$, $P < .025$). No correlation was found between glycemic rise and basal glucose ($r = .18$) or administered dose of insulin ($r = -.29$). When we examined whether a relationship existed between the duration of diabetes per se and glycemic restoration after hypoglycemia (15-minute increments in plasma glucose level or a 30-minute area under the curve), we found only a poor correlation ($r = -.377$), which did not achieve statistical significance.

Cardiovascular Variables

The mean resting pulse rate did not differ between the eight patients with glucagon increments within the normal range (64 ± 6 beats per minute) and patients with blunted glucagon rises (68 ± 9). When, however, resting pulse rates were compared between patients who had had diabetes for ten years or less and those who had had the disease for a longer duration, a significant difference was noted: 62 ± 5 beats per minute versus 73 ± 7, $P < .005$. Pulse rate increments during hypoglycemia did not differ in the two groups: 28 ± 10 beats per minute in the shorter duration patients versus 24 ± 6. No patients had on standing a drop in systolic blood pressure of more than 10 mm of mercury. The Valsalva ratio was 1.56 in patient 2, 1.4 in patient 3 and 1.3 in patient 6, values of 1.21 or greater being considered normal.[18]

Growth Hormone and Cortisol Responses to Hypoglycemia

The basal serum growth hormone level was 4.2 ± 2.4 ng per ml in normal subjects and 4.2 ± 2.2 in patients with diabetes. The respective increments after hypoglycemia were 44 ± 18 versus 39 ± 24 (not significant). The basal plasma cortisol level was 16 ± 4.7 μg per dl in controls and 16 ± 5.2 in patients with respective increments after hypoglycemia of 21 ± 7 versus 16 ± 9 (not significant).

Discussion

During this investigation on counterregulatory events in patients with type I diabetes for various durations, three observations were made: (1) an increasing duration of diabetes is accompanied by a progressive blunting of the glucagon response to insulin-induced hypoglycemia, (2) factors other than the duration of diabetes per se must contribute to the subnormal rises because these are occasionally noted in patients with only a few years of disease and (3) the capability to restore plasma glucose levels is significantly correlated with the capability to mount a glucagon response to hypoglycemia and both are severely compromised in patients with diabetes for more than ten years.

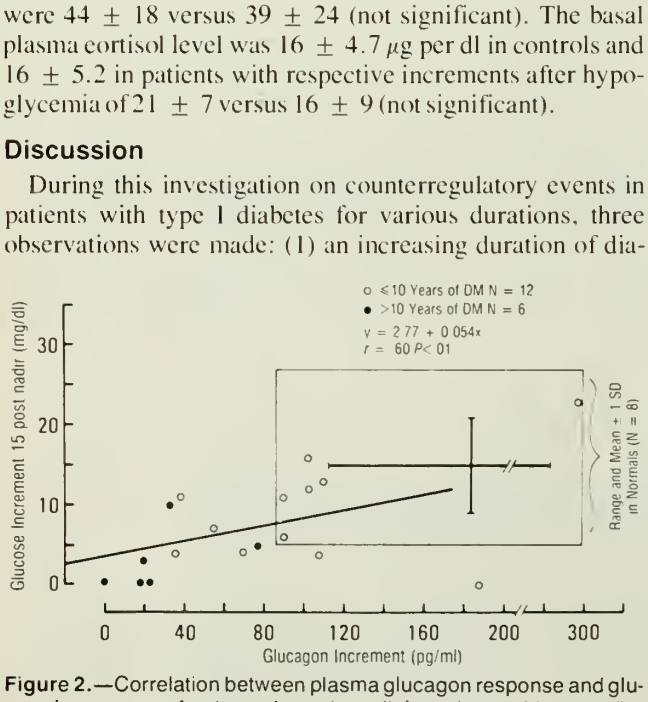

Figure 2.—Correlation between plasma glucagon response and glucose increments after hypoglycemic nadir in patients with type I diabetes mellitus (DM). The rectangle encompasses the range of responses in normal control (glucagon along the abscissa, glucose along the ordinate). SD = standard deviation.

Several considerations militate against the possibility that the progressively blunted or absent glucagon response to hypoglycemia might be accounted for by experimental variables. Basal glycemic levels are unlikely to be of relevance since the same blunted or absent glucagon responses to hypoglycemia have been found in diabetic patients studied after overnight return to normal of the plasma glucose level[11] or long-term improvement of metabolic status.[7] Furthermore, inducing hyperglycemia before the insulin tolerance test in normal subjects may delay, but does not impair, the glucagon response to hypoglycemia.[8,19] And this is despite the additional facts that to achieve hypoglycemia after inducing hyperglycemia, larger and multiple doses of insulin are required, glucagon levels become transiently suppressed and plasma glucose levels fall at a slower rate.[18] In agreement with the above observations in normal persons are the present findings in diabetic patients of absent correlations between metabolic variables and glucagon increments after hypoglycemia. Moreover, the glucagon response to hypoglycemia in patients with diabetes for more than ten years was significantly lower than in patients with the disease for a shorter duration, despite the fact that concurrent metabolic variables did not show a statistical difference.

The decreased glucagon response to hypoglycemia with increasing duration of type I diabetes could be regarded as a "complication" whose cause and pathogenesis are, however, not clearly defined. Loss of α-cell secretory capacity cannot be implicated since the same patients who are "nonresponders" to insulin hypoglycemia instead manifest glucagon hyperresponsiveness to other stimuli; autonomic neuropathy might exacerbate the defect[10] but is by no means a necessary determinant. In fact, in the absence of any sign of vagal and sympathetic neuropathy, many diabetic patients do not have a normal glucagon response to hypoglycemia.[7,10] Among our patients nonresponders did not show resting tachycardia or abnormal responses to Valsalva's maneuvers—accepted indices of parasympathetic dysfunction[18]—and no one suffered from sufficient loss of sympathetic function to cause postural hypotension. It has been observed that patients with the best preserved glucagon response to hypoglycemia have the most residual β-cell function.[20,21] Insulin secretory reserve has been shown to deteriorate with an increasing duration of diabetes[22] and the temporal pattern parallels quite closely the time course of deterioration of glucagon response to hypoglycemia observed in our study. Although the mechanism of a causal relationship, if any, between the two phenomena remains at this time speculative, it could be hypothesized that disappearance of the prevailing type of islet cells (β-cells) or the very processes leading to such disappearance[23] may, for architectural or direct pathogenetic reasons, disturb neighboring cells or local integrating systems important for

normal responses to hypoglycemia. In such a case, the compromised glucagon response to hypoglycemia would be a complication of the pathogenesis of type I diabetes rather than of long-term metabolic derangement and even tight glycemic control since the onset of diabetes might not succeed in fully preventing the abnormality. Only prospective studies in patients under meticulous control will help isolate structural from metabolic causes.

The important contribution of glucagon to brisk counterregulation was confirmed in our patients by the correlation found between glucagon responses to hypoglycemia and plasma glucose increments. However, glucagon response was not the only determinant toward restoration of plasma glucose. Two patients with substantial glucagon increments did not have an appropriate increase in their plasma glucose levels; they may belong to the category of patients who have delayed disappearance of insulin caused by insulin antibodies.[11] In the few patients whose plasma glucose level rapidly rose despite subnormal glucagon responses, this most likely occurred through an augmented compensatory epinephrine discharge.[24,25] Such multifactorial contributions to glucose counterregulation probably account for the fact that the correlation between glucagon and glucose responses was not absolute and that we could not identify a significant correlation between the duration of diabetes per se and the magnitude of the glycemic response. The fact, however, that eight of the nine patients showing a brisk glycemic increment had diabetes for fewer than ten years may be taken as a warning that beyond this duration of diabetes the crucial safety mechanisms—which do not include growth hormone and cortisol—become generally less efficient. This is in agreement with the finding by White and associates,[13] whose patients with inadequate counterregulation had no responses of either glucagon or epinephrine after a duration of diabetes of 15.9 $\pm$ 2.8 years (mean $\pm$ standard error of the mean).

At least two clinical implications can be drawn from these studies. The first is that because the glucagon response to hypoglycemia may be lost quite early, the effectiveness of the epinephrine response should be safeguarded. In particular, since the contribution of epinephrine to counterregulation is mediated through β-adrenergic receptors,[25,26] β-adrenergic blockers should be used with caution. The second clinical implication is that because the capability for counterregulation tends to decline with a progressive duration of diabetes, targets and modalities of treatment need to be periodically reassessed, possibly in a preventive fashion. These considerations should by no means halt attempts at ameliorating the metabolic status of diabetic patients; among other benefits, good diabetic control may result in improved glucose recovery from hypoglycemia, possibly by increasing the activity of liver enzymes involved in glycogenolysis and gluconeogenesis.[27] Special caution should, however, be exercised in the approach to patients with long-standing disease.

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Nd-YAG Laser Treatment of Tracheal Stenosis

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We administered Nd-YAG laser treatments in four patients aged 56 to 68 years for severe tracheal stenosis, the tracheal diameters varying between 2.5 and 5 mm. These patients were all dyspneic at rest with talking or dressing and their peak flows ranged from 8% to 36% of predicted. They were not felt to be candidates for surgical excision. Immediate palliative relief was achieved in all patients and lasted two to four months after a single treatment in three patients. One patient died three weeks after laser treatment due to respiratory failure from underlying emphysema. There were no complications of laser therapy. Postlaser therapy the tracheal diameter in each patient was at least 9 mm and peak flow improved to between 25% and 76% of predicted. The results suggest that laser treatment may be beneficial in cases of severe tracheal stenosis.

(Gelb AF, Epstein JD: Nd-YAG laser treatment of tracheal stenosis [Clinical Investigation]. West J Med 1984 Oct;141:472-475)

Society today is placing greater emphasis on justifying monetary expenditures in health care delivery, especially with new technologies. In this article we address the issue of the clinical appropriateness of the neodymium-yttrium-aluminum-garnet (Nd-YAG) laser in the treatment of advanced nonmalignant tracheal stenosis when no other rational medical or surgical approach is feasible. Results indicate that Nd-YAG laser treatment may provide immediate and temporary palliative relief.

Materials and Methods

The Nd-YAG laser (Medilas, MBB, Endo-lase, Inc, Washington, DC) generates a timed output of up to 80 to 100 W in the infrared wavelength—1,064 nm—which is conducted by a flexible quartz monofilament. The techniques we used are similar to those previously reported.[1]

Our indications to administer the laser treatment included a partially obstructed trachea that has not responded to mechanical dilatation in patients with uncontrolled cough, stridor and unrelenting dyspnea. These patients were felt to be too dyspneic to undergo an attempt at surgical excision of the stenotic area. Detailed informed consent was obtained from each patient, consistent with guidelines from the manufacturer's specifications and the US Food and Drug Administration, the California Patient's Bill of Rights and the local hospital institutional review committee. Immediate palliative improvement was determined by enlargement or recannulation of a previously obstructed trachea with relief of dyspnea, cough and stridor and associated physiologic improvement.

Before laser therapy we measured the patient's Dyspnea Index[2] and modified it so that a Dyspnea Index of 1 is shortness of breath only on climbing stairs, 2 is inability to walk a mile on level land at a normal pace, 3 is shortness of breath on walking 100 yd on level land and 4 is shortness of breath with slight exertion after dressing or talking. Pulmonary function studies (WE Collins, Inc, Braintree, Mass) and maximal expiratory and inspiratory flow volume loops were measured before and one day after laser therapy and results compared with previously published standards.[3-7]

Results

The four patients who underwent laser surgical treatment were extremely dyspneic with cough and stridor at rest. In each patient tracheal stenosis developed as a result of endotracheal intubation or tracheostomy (or both) done 4 to 24 months previously for management of repeated episodes of respiratory failure due to emphysema (cases 1 and 4) or congestive heart failure (cases 2 and 3). The patient in case 1 required repeat endotracheal intubation and mechanical ventilation before the laser therapy. Results of the pulmonary function studies are given in Table 1 and indicate severe

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TABLE 1.—*Results of Routine Pulmonary Function Studies in Patients With Tracheal Stenosis* *

Patient	Sex	Age Years	D_LCO (ml/min/mm Hg)	TLC Liters	PF Liters/sec	FEV_1 Liters prelaser	FVC Liters	V_{50} Insp Liters/sec	V_{50} Exp Liters/sec	PF Liters/sec	FEV_1 Liters	FVC Liters postlaser	V_{50} Insp Liters/sec	V_{50} Exp Liters/sec
1	♀	68	NA	NA	0.3 (0.08)†	0.2 (8)	1.2 (35)	0.8 (17)	0.1 (2)	1.0 (25)	0.3 (13)	1.3 (38)	1.2 (26)	0.4 (9)
2	♀	56	7 (37)	2.5 (50)	1.8 (36)	1.0 (47)	1.1 (34)	0.9 (19)	1.6 (34)	3.8 (76)	1.1 (52)	1.1 (34)	4.0 (85)	3.4 (72)
3	♂	68	25 (110)	5.0 (94)	1.7 (24)	1.4 (56)	2.7 (89)	0.7 (15)	1.7 (36)	4.9 (70)	2.3 (92)	2.7 (87)	2.3 (49)	3.0 (64)
4	♀	60	11 (65)	3.2 (83)	0.7 (13)	0.7 (58)	1.1 (48)	0.6 (13)	0.7 (15)	1.7 (34)	0.8 (65)	1.2 (50)	1.0 (21)	1.2 (26)

D_LCO = single breath diffusing capacity of lung, TLC = total lung capacity, PF = peak flow on forced expiration, FEV_1 = forced expiratory volume in 1 sec, FVC = forced vital capacity, V_{50} = maximal flow at 50% forced inspiration (Insp) or 50% forced expiration (Exp), NA = not available.

*Results before and one day after laser treatment.

†Percent predicted.

abnormalities. This is best noted in the maximal expiratory and inspiratory flow volume loops as shown in Figure 1. The pulmonary function studies in patient 1 show severe variable intrathoracic tracheal airflow limitation superimposed on severe emphysema. Patient 2 shows a severe inspiratory air flow plateau consistent with variable extrathoracic tracheal obstruction superimposed with congestive heart failure and diffuse pleural thickening. In case 3, there were as severe inspiratory and expiratory flow limiting plateaus, consistent with a variable extrathoracic tracheal obstruction in a patient with underlying congestive heart failure. Case 4 shows flow plateaus similar to those in case 3 in a patient with underlying emphysema. All of the patients were extremely dyspneic on just talking or dressing, consistent with a Dyspnea Index of 4.

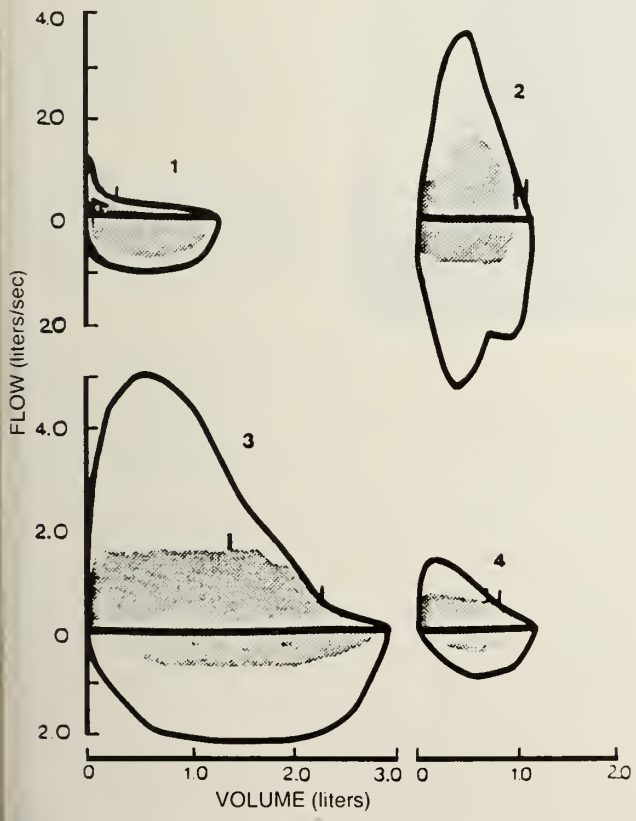

Figure 1.—Maximal flow volume loops on both expiration (above the horizontal 0 flow line) and inspiration in cases 1, 2, 3 and 4 before (shaded area) and one day after laser therapy. Age-corrected normal values[3] for 50% of expired forced vital capacity are 4.7 liters per second, ± 0.7 (mean ± 1 standard deviation) and for 25% of expired forced vital capacity 1.8 liters per second, ± 0.4. Values for inspiratory flow are similar. The slashed line on the expiratory loops mark off the forced expiratory volume in one second (see Table 1).

The location of the tracheal stenosis in patient 1 was a diaphragmatic web 2.5 cm below the vocal cords with a resulting tracheal diameter of 5 mm. The stenosis in patient 2 was 1.5 cm below the vocal cords and extended 1 cm inferiorly in a concentric manner with a tracheal diameter of 3.5 mm. In patient 3 the concentric stenosis began 2 cm below the vocal cords and extended 1.5 cm inferiorly with a tracheal diameter of 2.5 mm. Patient 4's stenosis began 3 cm below the vocal cords and extended 1 cm inferiorly with a tracheal diameter of 5 mm. This patient with severe emphysema had pronounced instability of the trachea and major airways.

After a single laser treatment the tracheal diameter in each patient increased to at least 9 mm (see Figures 2 and 3) with improvement in pulmonary function that may be best appreciated in the maximal expiratory and inspiratory flow volume loops (see Table 1 and Figure 1). Clinically the Dyspnea Index improved to 3 in patient 4 and to 2 in patients 2 and 3 and has persisted up to two to four months postoperatively after a single treatment. Patient 1's endotracheal tube was successfully removed but she subsequently died of recurrent respiratory failure three weeks after the laser therapy. Patient 2 required repeat laser therapy two months following the initial procedure, and similarly good results were achieved. There were no complications associated with the laser procedure.

The operative procedure and related overnight hospital and physician costs are estimated at $3,000 per laser treatment. For comparison, the average cost for a one-day hospital stay in the greater Los Angeles area is $1,000.

Discussion

The results of this study show that the Nd-YAG laser provided immediate palliative relief in four symptomatic patients with severe tracheal stenosis associated with life-

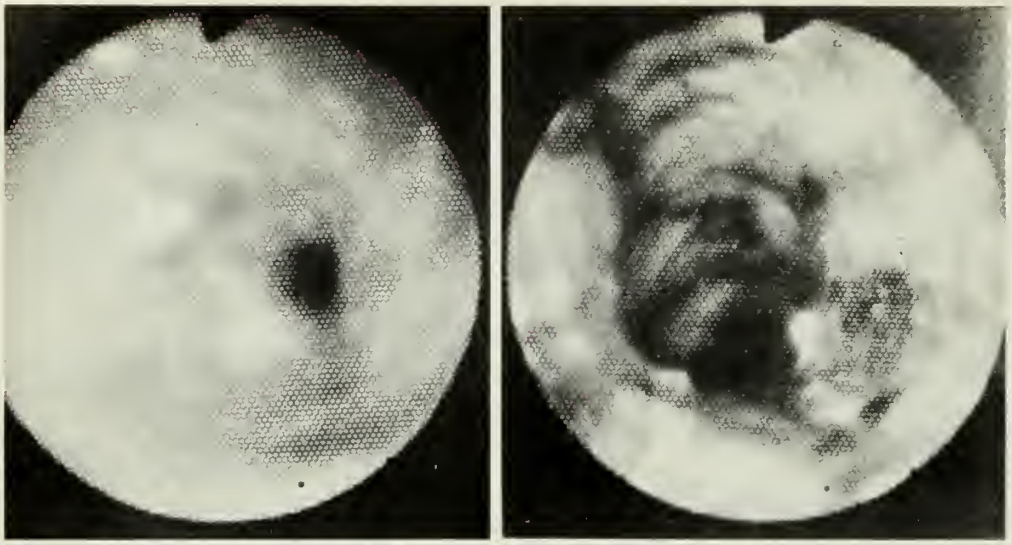

Figure 2.—Tracheal stenosis in patient 3 before (left) and immediately after (right) laser therapy. Diameter was increased from 2.5 to 10 mm.

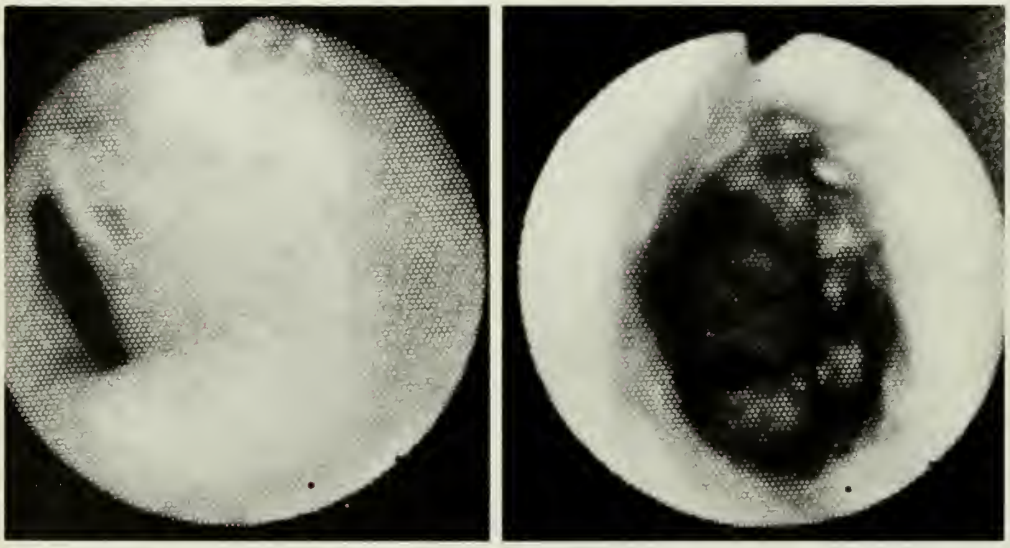

Figure 3.—Tracheal stenosis in patient 4 before (left) and immediately after (right) laser therapy. Diameter was increased from 5 to 11 mm.

threatening cough, stridor or dyspnea. Furthermore, there existed no rational alternative therapy as previous attempts at mechanical dilatation had failed and the stenosis was felt to be too advanced for surgical excision in these already compromised patients. The diagnostic decision to consider superimposed tracheal stenosis in a patient already dyspneic and compromised by chronic cardiac or respiratory failure or both is difficult. However, it should be considered in the setting of previous endotracheal intubation or tracheostomy, especially with the development of an inspiratory stridor or unexplained cough. While the results of pulmonary function studies in these patients are often abnormal, the development of low-flow plateaus on the maximal inspiratory or expiratory flow volume loops may suggest intrathoracic or extrathoracic tracheal stenosis.[7] The diagnosis can only be confirmed by bronchoscopy, but a chest roentgenogram or tracheal tomography may be helpful.

The treatment of tracheal stenosis is complex and challenging. Usually, in milder instances mechanical dilatation with rigid bronchoscopy may suffice, whereas in more advanced stages, excision of stenotic areas followed by reconstruction may be required. Most recently, endoscopic methods using carbon dioxide and Nd-YAG lasers have provided therapeutic alternatives to traditional surgical methods.

Tracheal stenosis from endotracheal intubations or tracheostomy may result in various complications. Least troublesome are localized granulomas, though at times they may reach considerable proportions. More troublesome is the outgrowth of a fibrous web or diaphragm. Moreover, the fibrous tissue may extend longitudinally to involve more of the trachea. The most complicated variant includes involvement of the tracheal wall itself with erosion and possible fracture of the cartilaginous rings and collapse.

In the present study all of the patients had either a diaphragmatic web or longitudinally extended stenosis that spared the tracheal wall itself, allowing it to maintain its stability. This type of stenosis should be most responsive to cure by laser therapy.[8,9] For cases of more advanced tracheal stenosis including collapse, Toty and co-workers[8] reported that after a 6- to 18-month follow-up, 8 of 17 patients treated with the Nd-YAG laser required additional surgical reconstruction. An incidence of only 50% improvement was also noted by Dumon and associates[9] using the Nd-YAG laser and

33% by Simpson and colleagues[10] using the carbon dioxide laser in six cases. Selected patients may ultimately require a Montgomery tube for stabilization or sleeve resection.

Whereas there were no complications in the present laser series, it would be anticipated that complications could occur, similar to those in laser treatment of endobronchial tumors.[1,8,9,11,14] It is too early to compare the effectiveness of the carbon dioxide and Nd-YAG laser techniques. Toty and co-workers[8] and Dumon and associates[9] developed the pioneering techniques that allowed Nd-YAG laser bronchoscopy to clinically mature. They both favor the use of the rigid bronchoscope to deliver the laser fiber and to provide better access. The drawback, however, is the need for deeper anesthesia, which may result in further respiratory compromise. Brutinel and colleagues[13] have documented the deterioration of gas exchange during laser therapy. While the fiberoptic bronchoscope may be adequate in many cases, the rigid bronchoscope is necessary and mandatory to remove large pieces of coagulated tissue that are obstructing the trachea. We favor the use of both fiberoptic and rigid bronchoscopy with intravenously administered sedatives and the patients breathing on their own.

Finally, we must consider the issue of the clinical justification of this relatively expensive procedure. It appears to offer excellent palliative relief in patients with tracheal stenosis with life-threatening dyspnea, cough or stridor who have severe air-flow limitation, cases for which there currently exists no other medical alternative. Optimal results may ultimately require additional surgical procedures but the initial goal is to provide an adequately patent trachea for ventilation. The use of the laser for the treatment of benign tracheal stenosis complements its established use in treating endobronchial malignant tumors.[1,8,9,11,14] Furthermore, the cost of laser treatment is far less than the accumulative cost of a lengthy hospital stay for an asphyxiating patient for whom no other reasonable therapeutic alternative exists.

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Hypertension—Indications, Goals and Potential Risks of Drug Therapy

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Double-blind, placebo-controlled studies show that drug treatment of hypertension does not significantly reduce morbidity and mortality at diastolic pressures less than 105 mm of mercury. Nevertheless, most physicians start drug therapy at 90 to 104 mm of mercury. Few reports have dealt with the level to which blood pressure should be reduced. Available data, including reports from two large-scale studies, suggest that excessively low diastolic pressure due to drug therapy may cause an increase in deaths from coronary heart disease. Other studies suggest that reducing diastolic pressure below 100 mm of mercury does not enhance the prevention of complications of hypertension nor the reversal of pretreatment secondary change. Therefore, it is suggested that drug treatment of hypertension should be begun only if diastolic pressure is consistently 105 mm of mercury despite hygienic measures of treatment. A goal diastolic pressure of at least 100 mm of mercury is suggested.

(Aagaard GN: Hypertension—Indications, goals and potential risks of drug therapy. West J Med 1984 Oct; 141:476-480)

Hypertension continues to be one of our most prevalent health problems. It confronts physicians with the need to decide at what blood pressure level drug therapy should be started. This decision should be based on studies showing that the morbidity and mortality of hypertension is reduced by drug treatment. To be a valid basis for this decision, a study must be double-blind and placebo-controlled. Randomly assigned subjects must be observed under treatment conditions that are identical except for the active drug versus placebo feature. Studies that meet these standards were conducted by the Veterans Administration Cooperative Study Group[1] and the US Public Health Service Hospitals Cooperative Study Group[2] and showed no significant benefit from drug treatment of hypertension in subjects who had entry pressures of 90 to 104 mm of mercury diastolic. Nevertheless, many physicians prescribe antihypertensive drugs for patients whose pressures are in this range. A mail survey of health care providers conducted in New York City in 1978 showed that 92% initiated drug therapy at 90 to 104 mm of mercury diastolic pressure.[3] This was probably the result of an intense educational campaign conducted over several years with its goal to encourage early recognition and treatment of hypertension.

Publication of the report of the Hypertension Detection and Follow-up Program (HDFP)[4] in 1979 added fuel to the fire. It stated, "thus, for the first time, with the large sample size of HDFP, evidence has been obtained on the efficacy of antihypertensive pharmacologic treatment for adults with mild BP elevation." The HDFP report has been widely quoted to support active drug treatment of mild hypertension.

Because there appears to be some difference between the current practice of many physicians and the evidence of properly designed studies, and because most newly recognized hypertensive patients are in the 90 to 104 mm of mercury diastolic range, it is important to review pertinent data that may be helpful in answering the following questions:

- At what blood pressure level is drug treatment effective in reducing morbidity and mortality of hypertension?
- To what level should blood pressure be reduced if drug treatment is initiated?
- Does drug treatment of hypertension contribute to an increased incidence of myocardial infarction or other manifestations of coronary heart disease?

Blood Pressure Level at Which Drug Treatment Reduces Morbidity and Mortality

Veterans Administration Cooperative Study

This study was double-blind and placebo-controlled. All subjects were studied in the hospital for at least six days and

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ABBREVIATIONS USED IN TEXT

HDFP = Hypertension Detection and Follow-up Program
MRFIT = Multiple Risk Factor Intervention Trial
RC = referred care (group)
SC = stepped care (group)
SI = special intervention (program)
UC = usual (health) care (source)
USPHS = United States Public Health Service Hospitals Study

were accepted into the study only if diastolic pressure averaged 90 mm of mercury or more during days four to six in hospital. Subjects were observed as outpatients for a prerandomization period of two to four months during which they received a placebo. Diastolic pressures during the last two clinic visits were the basis for the entry blood pressure classification of subjects. Men with diastolic pressures averaging 90 to 114 mm of mercury were admitted to the study. Without placebo treatment, the entry blood pressure range of these subjects might well have been 95 to 119 mm of mercury.

The average duration of follow-up was 3.3 years for the placebo-controlled subjects and 3.2 years for the drug-treated subjects. Blood pressure change was reported after four months of treatment and showed an average diastolic increase of 1.2 mm of mercury in the control subjects and an average decrease of 17.4 mm of mercury in the treated subjects, a difference of 18.6 mm of mercury.

In the evaluation of the results of drug treatment of hypertension, it is important to consider the changes in blood pressure which were allowed before placebo subjects were disqualified and removed from the study. In the Veterans Administration study of mild to moderate hypertension, subjects were removed from the study if diastolic pressure exceeded 124 mm of mercury on three separate clinic visits and persisted for three weeks or longer. Twenty control subjects were removed from the trial for such an excessive blood pressure increase. They had not experienced any complication at the time of removal from the study.

The incidence of complications in subjects whose entry diastolic pressures were 90 to 104 mm of mercury was not significantly higher in the control subjects than in the treated group. On the other hand, there was a significant reduction in complications in the drug-treated subjects with entry blood pressures of 105 to 114 mm of mercury. When complications were examined by diagnostic categories in subjects with entry diastolic pressures from 90 to 114 mm of mercury, there was no significant difference between treated and control subjects in myocardial infarction or sudden death, regarded as manifestations of coronary heart disease.

In summary, in the Veterans Administration study no significant reduction in overall complications or in complications related to coronary heart disease was noted in the drug treated subjects with entry diastolic pressures of 90 to 104 mm of mercury. This was true despite the fact that these subjects, for reasons noted above, were probably more severely hypertensive than the entry diastolic pressure would suggest and diastolic pressure was permitted to increase to as high as 124 mm of mercury before subjects were removed from the study.

The US Public Health Service Hospitals Study

In this study, subjects were free of any evidence of secondary hypertensive change on entry to the study. Baseline blood pressure was determined by averaging readings made during a three-month single-blind placebo trial period. Subjects were excluded if diastolic pressure fell to less than 90 mm of mercury on two of the three visits. Subjects were then randomly assigned to active or placebo treatment and followed in double-blind fashion. The study was planned for seven to ten years, average follow-up was eight years. Eighty percent of subjects had baseline diastolic pressure of 90 to 104 mm of mercury; 20% had 105 to 114 mm of mercury.

It is likely that the prerandomization placebo therapy reduced the entry blood pressure slightly. It is important to note that subjects continued in the study unless diastolic pressure exceeded 130 mm of mercury for three visits over a one-month period (6% of the subjects were excluded for that reason during follow-up, but had no other complication at the time of removal from the study).

On the average, diastolic pressure was 10 mm of mercury lower throughout the study for treated subjects. There was no reduction in deaths or manifestations of coronary heart disease in treated subjects. There was a reduced incidence of morbid events in the treated subjects (29.0%) as compared with placebo subjects (45.9%). Most of this difference was accounted for by electrocardiographic evidence of hypervoltage or left ventricular hypertrophy or chest x-ray indications of increased myocardial afterload. The report concludes by suggesting that patients with mild hypertension should receive careful follow-up supplemented by hygienic intervention (weight control, salt restriction, smoking cessation and exercise), and states "it is appropriate to consider deferral of drug therapy . . . until electrocardiographic changes, such as hypervoltage or ventricular hypertrophy are present."

In summary, the USPHS study of mild hypertension (diastolic pressure of 90 to 104 mm of mercury but with 20% of subjects at 105 to 114 mm of mercury on entry), in which subjects were observed for seven to ten years and blood pressure elevations as high as 130 mm of mercury diastolic were permitted, showed no significant difference in deaths or major complications as a result of drug treatment.

The Hypertension Detection and Follow-up Program

The Hypertension Detection and Follow-up Program (HDFP) was not a double-blind, placebo-controlled study. It compared care given in special HDFP centers—stepped care (SC)—with care given in community hospitals and clinics and in physicians' offices—referred care (RC). It did not compare drug treatment with placebo. A significant number of subjects in both groups received antihypertensive drugs.

The conditions under which subjects were followed during the five-year study were far from identical. SC subjects received intensive supportive care as a part of a team effort, the sole purpose of which was to keep them under antihypertensive care. In some of the clinics, vans picked up the subjects at home and transported them to and from the clinic. Subjects were seen promptly at clinic visits. Subjects who failed to keep appointments were called to reschedule. In some

clinics, babysitters were provided for subjects with children. In other clinics, arrangements were made so that employed subjects could attend without loss of pay. A physician was available by phone 24 hours a day to answer questions. The SC subjects were the beneficiaries of an intensive psychological and social support system throughout the five-year follow-up period.

The RC subjects received care in a variety of facilities which included clinics in large hospitals for the indigent, as well as the offices of physicians in practice.

HDFP subjects were classified by entry diastolic pressure as follows: stratum I—90 to 104, stratum II—105 to 114, stratum III—at least 115 mm of mercury. The endpoint for the study was mortality. In stratum I, overall mortality was reduced in SC as compared to RC by 20%. Mortality from myocardial infarction was reduced in SC by 46%. Mortality from cerebrovascular disease was reduced by 45%. These results are in striking contrast to those of the Veterans Administration and USPHS studies.

What is the explanation for the difference in mortality in HDFP? It cannot be attributed to drug treatment since a significant number of both SC and RC subjects received drugs. Could the difference be due to blood pressure level during treatment? Treatment diastolic blood pressure for SC averaged only 5.4 to 4.3 mm of mercury lower than RC during the years of the study. This is much less of a blood pressure difference between treatment groups than that in the VA study, 18.6 mm of mercury, and in the USPHS study of 10 mm of mercury. Therefore, difference in treatment blood pressure does not seem to be an explanation for the difference in myocardial infarction, cerebrovascular deaths and overall mortality.

It is possible that the strong psychological and social support given the SC subjects over the five-year study caused the reduction in mortality. Whatever the cause, it is important to note that it appeared to have a favorable effect in SC on mortality from myocardial infarction, cerebrovascular disease and overall deaths.

In summary, evidence from double-blind, placebo-controlled studies shows that drug treatment of hypertension does not significantly reduce morbidity and mortality at diastolic pressures below 105 mm of mercury. Therefore, unless symptoms are present which appear to be related to the elevated blood pressure, drug therapy should not be initiated unless diastolic pressure is consistently 105 mm of mercury or greater.

To What Level Should Blood Pressure Be Reduced by Drug Therapy?

Few studies of drug treatment of hypertension have considered the possible influence of the level to which blood pressure is reduced. Taguchi and Freis[5] reported on the effect of partial reduction of blood pressure in the subjects of the Veterans Administration study of mild to moderate hypertension. Drug-treated subjects with entry blood pressures of 90 to 114 mm of mercury diastolic were classified according to their average diastolic pressure after 4, 8 and 12 months of treatment. Subjects in the higher group all had an average diastolic pressure of 90 mm of mercury or greater, with a group average of 96. Subjects in the lower group all had average diastolic pressure of less than 83 with a group average of 79 mm of mercury. The attack rates of complications were almost identical: 12.1% in the group with higher treatment diastolic pressures and 11.5% in the lower group.

The effect of degree of blood pressure reduction on improvement of objective evidence of secondary hypertensive change was studied by Dorph and co-workers.[6] They recorded improvement in retinal abnormalities, decrease in heart size as measured by x-ray film taken at 1.5 meter focal distance, improvement in electrocardiographic abnormalities and decrease in serum creatinine. They reported mean blood pressure and used normal values which increased with age. The blood pressure response was considered unacceptable if blood pressure remained greater than 133% of normal, acceptable from 121% to 133% of normal, and good if 120% of normal or less. They found that patients whose pressure was reduced to less than 133% of normal had significantly more improvement than those in whom pressure remained above 133% of normal. However, the amount of improvement was not greater in patients whose pressure was reduced to 120% of normal or less than it was in patients in the range 121% to 133% of normal. Their results suggest that improvement of secondary objective findings of hypertension was not enhanced by reducing diastolic pressure below 133% of normal or below 101 mm of mercury at age 30 to 39 years; below 106 mm of mercury at age 40 to 49 years, and below 115 mm of mercury at age 50 to 64 years.

In summary, the Veterans Administration study suggests that a drug treatment goal of 90 to 100 diastolic would be effective in preventing complications. The report of Dorph and co-workers suggests that this goal might be lower than is necessary to improve funduscopic pathology, to lower creatinine, to reduce heart size and to reverse hypertensive electrocardiographic changes. Their studies further suggest that the diastolic pressure treatment goal should be higher in older patients.

Does Drug Treatment of Hypertension Contribute to an Increased Incidence of Myocardial Infarction or Other Manifestations of Coronary Heart Disease?

In this section, three studies will be reviewed which suggest that the incidence of myocardial infarction or other manifestations of coronary heart disease may be increased in patients receiving antihypertensive drug therapy. Stewart[7] observed 169 hypertensive patients for an average of 6.25 years. He noted the diastolic pressure on the visit before myocardial infarction occurred and called it final diastolic pressure. He found that patients with a final diastolic pressure below 90 mm of mercury had a 5.4 relative risk of infarction compared with 1.0 relative risk for patients at 100 to 109 mm of mercury.

When he limited his analysis to 102 patients whose blood pressure was stable through the treatment program, he found that the relative risk of myocardial infarction was 6.4 at final diastolic pressure of 76 to 94, 1.0 at 95 to 109 and 2.7 at 110 to 140 mm of mercury.

Next he studied the patients with myocardial infarction and final diastolic pressure of 100 mm of mercury or less. He matched them with patients without infarction, but with similar entry diastolic pressure and other risk characteristics.

Entry diastolic pressures averaged 123.0 in the 14 patients with infarction and 123.4 mm of mercury in the patients without infarction. He found that the average blood pressure reduction in the infarction patients was 35.5 (28.9%) compared to 20.4 mm of mercury (16.5%) for the matched patients without infarction.

Stewart suggests that blood pressure reduction in moderate to severe hypertension should be by no more than 22% of beginning diastolic pressure or to around 104 to 110 mm of mercury.

The HDFP report on subjects in stratum II, entry diastolic pressures 105 to 114, and stratum III, entry diastolic pressures 115 mm of mercury or greater, shows 38% more deaths from myocardial infarction in SC subjects in strata II and III combined as compared with RC subjects. Table 1 shows that the average diastolic pressure in stratum II was reduced by 19.3 to 23.4 (17.8% to 21.6% of entry pressure) in SC compared with 11.3 to 18.0 mm of mercury (10.4% to 16.5% of entry pressure) in RC. In stratum III the difference in the degree of blood pressure decrease was even more striking: 28.2 to 34.6 (23.1% to 28.4%) in SC, 19.2 to 28.1 mm of mercury (15.7% to 23.0%) in RC.

It is important to note that the increase in SC deaths from myocardial infarction occurred despite the intensive psychological and social support system that SC subjects received. Deaths from cerebrovascular disease are 42.8% lower in SC than in RC in strata II and III. This is similar to the degree of reduction of cerebrovascular deaths noted in SC in stratum I. This suggests that excessive blood pressure reduction in SC subjects not only negated the benefits of the intensive support system, but caused an increase in deaths from myocardial infarction. This hazard does not appear to apply to deaths from cerebrovascular disease.

The report of the Multiple Risk Factor Intervention Trial (MRFIT)[8] also suggests that drug treatment of hypertension may increase death rate from coronary heart disease. In MRFIT, men at high risk for coronary heart disease were randomly assigned to a special intervention program (SI) or their usual health care source (UC). The SI group received stepped-care treatment for hypertension, counseling to help them stop cigarette smoking and dietary advice for lowering blood cholesterol levels. The average follow-up period was seven years.

In the SI group previously untreated subjects with entry diastolic pressure greater than 90 mm of mercury were given antihypertensive drugs with a goal blood pressure of either a 10 mm of mercury reduction or to 89 diastolic pressure, whichever was lower. Subjects who were already receiving antihypertensive drugs and had an entry diastolic pressure of 90 or less were assigned a goal diastolic pressure of 80 mm of mercury. Subjects could be regarded as mild to moderate hypertensives since candidates were excluded from the study if diastolic pressures were 115 or greater at the first screening visit or 120 mm of mercury or more at the second screening visit.

It is important to note that SI and UC subjects did not receive identical care. SI subjects received counseling and participated in group discussions. Hypertensive SI subjects were seen frequently during the step-up phase of care until blood pressure was below goal pressure. They were the beneficiaries of a treatment program which gave psychological and social support.

Comparison of all hypertensive SI subjects with all hypertensive UC subjects shows no difference in coronary heart disease death rate. However, nonsmoking SI subjects with lower cholesterol and the highest level of blood pressure had an 81% lower coronary heart disease death rate than UC subjects. On the other hand, the mildest hypertensive subjects who are smokers with higher cholesterol levels showed a 17% decrease in coronary heart disease death rate in UC as compared with SI. These data suggest that the coronary heart disease death rate was reduced in subjects at highest blood pressure level by a treatment program that included antihypertensive drug therapy and the psychological and social support. It is reasonable to ascribe most of this decrease in coronary heart disease mortality to psychosocial support since both the Veterans Administration and the USPHS studies showed no change from drug treatment in coronary heart disease manifestations. More important, however, is the fact that subjects with the mildest degree of hypertension have lost the beneficial effects of the program and show an increase of coronary heart disease death rate in drug-treated subjects.

The MRFIT report gives data on the relationship of abnormal entry resting ECG to the differences in the coronary heart disease death rate. It was found that in subjects with hypertension and an abnormal entry electrocardiogram, the coronary heart disease death rate was 65% greater in the SI subjects. In hypertensive subjects, without electrocardiographic abnormalities on entry, the SI subjects had a 24% lower rate of coronary heart disease deaths. This suggests that antihypertensive drug therapy has an unfavorable effect on such mortality in subjects with electrocardiographic abnormalities.

TABLE 1.—*Hypertension Detection and Follow-up Program Average Diastolic Blood Pressure Response by Strata (mm of mercury)*

	Stratum I Entry DBP: 96.4		*Stratum II Entry DBP: 108.7*		*Stratum III Entry DBP: 122.3*	
	SC	*RC*	*SC*	*RC*	*SC*	*RC*
R_xDBP	86.4-83.4	91.9-87.8	89.1-85.0	97.4-90.7	93.5-87.1	103.1-94.2
△DBP	9.9-12.9	4.5- 8.6	19.3-23.4	11.3-18.0	28.2-34.6	19.2-28.1
%△	10.2-13.4	4.6- 8.9	17.8-21.6	10.4-16.5	23.1-28.4	15.7-23.0

SC = stepped care (group)
RC = referred care (group)
R_xDBP = mean resting diastolic blood pressure in years 1, 2, 4, 5 of study
△DBP = change in diastolic blood pressure from entry
%△ = percent change in diastolic blood pressure

There are other data in the MRFIT report suggesting that an excessively low goal for blood pressure during treatment might be a factor in the increased coronary heart disease mortality observed in some hypertensive SI subgroups. In the hypertensive subjects who were not receiving antihypertensive drug therapy on entry, the coronary heart disease mortality rates were 45% greater for SI subjects with entry diastolic pressure 90 to 94 and 30% lower for SI subjects with entry diastolic pressure 100 mm of mercury or greater. The SI group with the lowest blood pressure goal had an increased mortality from coronary heart disease, whereas the SI group with the highest blood pressure goal had a reduction in coronary heart disease mortality. It does not seem likely that the higher coronary heart disease mortality in SI subjects with entry diastolic pressure of 90 to 94 mm of mercury would be due to a higher frequency of abnormal electrocardiographic findings. One would expect that this group of subjects would have a lower frequency of abnormal findings on electrocardiograms than the group of subjects with entry diastolic pressure 100 mm of mercury or greater.

In summary, MRFIT results suggest that antihypertensive drug therapy given in concert with measures to help subjects to stop smoking and to lower blood cholesterol levels has an unfavorable effect on coronary heart disease mortality in mild hypertension and a beneficial effect at the higher levels in this study. The unfavorable effect appears to be greater in subjects with abnormal entry electrocardiographic findings and in subjects with lowest entry diastolic pressure (90 to 94) and hence with lowest diastolic pressure goals (80 to 84 mm of mercury). This unfavorable effect on coronary heart disease mortality is powerful enough to reverse the benefits of the total treatment program which are seen in SI subjects with the highest blood pressure levels.

Conclusions

The studies reviewed above suggest that antihypertensive drug therapy should not be initiated unless diastolic pressure is consistently 105 mm of mercury or greater. Below that level drug treatment gives no significant benefits, and may increase manifestations of coronary heart disease and may cause adverse symptoms.

The diastolic pressure goal of drug treatment should probably be from 90 to 100 mm of mercury. Reducing pressure below 90 mm of mercury does not appear to be beneficial and may do harm. If diastolic pressure is 90 or less in the office or clinic or 85 mm of mercury or less at home, a gradual decrease in dosage of antihypertensive drugs should be commenced. One method is to reduce the daily dose of one drug by 10% to 25% every two weeks as long as home diastolic pressure is 85 mm of mercury or less.

Although it is recommended that antihypertensive drug therapy be withheld unless diastolic pressure is consistently 105 mm of mercury or greater, it is not suggested that all treatment be withheld. Blood pressure should be followed at appropriate intervals in the office or home, or both. In addition, an intensive effort should be made to lower blood pressure through hygienic measures, dietary salt restriction, weight reduction in patients who are above ideal body weight, exercise appropriate to the age and physical condition of the patient and behavioral methods. Properly applied hygienic measures have no adverse effects and often increase the sense of well-being. They should be recommended for most patients with persistent hypertension and also for those with occasional hypertension.

It is encouraging to note that the course of diastolic pressure in mild hypertension is favorable or stable in most patients. The Australian Study[9] of mild hypertension was placebo-controlled, but not double-blind. Although it is not useful in determining the results of drug treatment, it does provide valuable data on the course of placebo-treated subjects. In that study, subjects had entry diastolic pressures of 95 to 109 mm of mercury. After three years of placebo follow-up, 48% of the subjects had diastolic pressure less than 95 mm of mercury, 30% remained 95 to 109 and 12% had greater than 109 mm of mercury.

Physicians should, therefore, have a positive and hopeful attitude in caring for patients with mild hypertension. Blood pressure should be followed at home or in the office. Hygienic measures of treatment should be utilized. Antihypertensive drugs should be prescribed in patients with diastolic pressure consistently above 105 mm of mercury.

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Gastrointestinal Symptoms of Marathon Runners

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A survey of 707 participants in the 13th Annual Trail's End Marathon in Seaside, Oregon, showed a high incidence of gastrointestinal disturbances, predominantly of the lower tract, associated with long-distance running. The urge to defecate, both during and immediately after running, occurred in over a third of runners. Bowel movements (35%) and diarrhea (19%) were relatively common after running, and runners occasionally interrupted hard runs or races for bowel movements (18%) or diarrhea (10%). Lower gastrointestinal disturbances were more frequent in women than in men and in younger than in older runners. Awareness of the frequency and nature of gastrointestinal symptoms documented by this survey will assist physicians in evaluating abdominal complaints in runners.

(Keeffe EB, Lowe DK, Goss JR, et al: Gastrointestinal symptoms of marathon runners. West J Med 1984 Oct; 141:481-484)

Jogging and running are popular forms of endurance exercise to achieve physical fitness, and participation in these activities has increased dramatically in recent years. The American College of Sports Medicine makes the following recommendations on the quantity and quality of training to develop and maintain cardiorespiratory fitness and body composition: frequency of exercise of three to five days a week, intensity at 60% to 90% of maximum heart rate reserve, duration of 15 to 60 minutes of continuous acrobic activity and any activity that uses large muscle groups.[1] Running is the most convenient exercise to achieve these goals and has introduced an increasing percent of the population to long-distance running, including the marathon. A recent comprehensive review of studies addressing metabolic and physiologic aspects of marathon running cites investigations involving most organ systems with the notable exception of the gastrointestinal (GI) tract.[2] Personal experience, numerous anecdotal reports from fellow runners (hoping a physician runner would be wise enough to prevent or at least explain their GI disturbances) and results of a small survey of members of a running club[3] suggest that GI symptoms associated with running are common and may even include bloody diarrhea.[4,5] To better document the frequency of GI disturbances experienced during or immediately after long-distance running, a questionnaire surveying GI symptoms was given to the 1,700 participants of the 13th Annual Trail's End Marathon in Seaside, Oregon.

Methods

A single-page questionnaire was included in the race packet of all entrants in the 13th Annual Trail's End Marathon, which took place at Seaside, Oregon, on February 27, 1982. Participants were told that the purpose of the survey was the collection of information from a large group of long-distance runners to better understand the effects of running on gastrointestinal tract function. Completed questionnaires were returned in accompanying self-addressed and stamped envelopes or left in a designated return box at the finish area.

The questionnaire addressed three areas: (1) demographic data, which included age, sex, years running and average weekly mileage; (2) baseline GI symptoms, which included the average number of daily bowel movements and the frequency of loose stools or abdominal cramps, and (3) symptoms associated with running, either during easy training runs (category A), during hard training runs or races (category B) or immediately after an easy or hard run (category C). Symptoms surveyed in each category included the upper GI tract symptoms of heartburn, nausea and vomiting, and the lower GI tract symptoms of abdominal cramps, urge to have a bowel movement, actual bowel movement, diarrhea and bloody bowel movement. Participants were asked to estimate the frequency of baseline and running-related GI symptoms by indicating whether each symptom occurred never, rarely, occasionally or frequently. Runners were also

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invited to provide anecdotal comments on the reverse side of the questionnaire.

For purposes of data analysis, a symptom was considered present (a positive response) when a respondent indicated "occasionally" or "frequently" and absent (a negative response) when "never" or "rarely" were indicated. To calculate the percent of respondents experiencing a given symptom, the "occasionally" and "frequently" responses were summed and divided by the total number of responses. Chi-square analysis was used to compare frequency of symptoms in each of the three running categories and differences between sex and age groups. Differences with a *P*-value equal to or smaller than .05 were accepted as statistically significant.

Results

Questionnaires were returned by 707 (41.6%) of the 1,700 participants in the Seaside marathon. Demographic data of the respondents are shown in Figures 1 and 2. Mean age of the respondents was 35.5 years, and nearly 90% were between ages 20 and 60 years, with ages 31 through 40 having the largest representation. Men constituted 85.5% of respondents. The weekly running mileage averaged 45.7 miles per week, and the mean number of years running was 5.9 years.

Responses to questions regarding baseline symptoms showed that 57% of respondents had one or less than one bowel movement daily, 30% had 2 bowel movements per day and 13% had three or more per day. Also, 15% had frequent and 45% occasional loose bowel movements, whereas only 2% had frequent and 16% occasional abdominal cramps.

The frequency of upper gastrointestinal tract symptoms experienced during or after running is displayed in Table 1. Heartburn was noted by 8.8% to 9.5% of runners and occurred significantly more often during than after running. Nausea and vomiting were significantly more common during hard runs or after running than during easy runs. Analysis of sex and age subgroups for each of these three symptoms showed no significant differences except that women had nausea more often than men during both easy and hard runs.

Table 2 displays lower gastrointestinal tract symptoms associated with running. Abdominal cramps were more common during hard runs (19.3%) or after running (13.9%) than during easy runs (10.9%). The urge to have a bowel movement was equally as frequent in all three categories and experienced by over a third of respondents (36.4% to 38.6%). During easy or hard runs 16% to 18.4% of respondents had bowel movements occasionally or frequently, 8.2% to 10% had diarrhea and 1.2% to 1.8% had a bloody

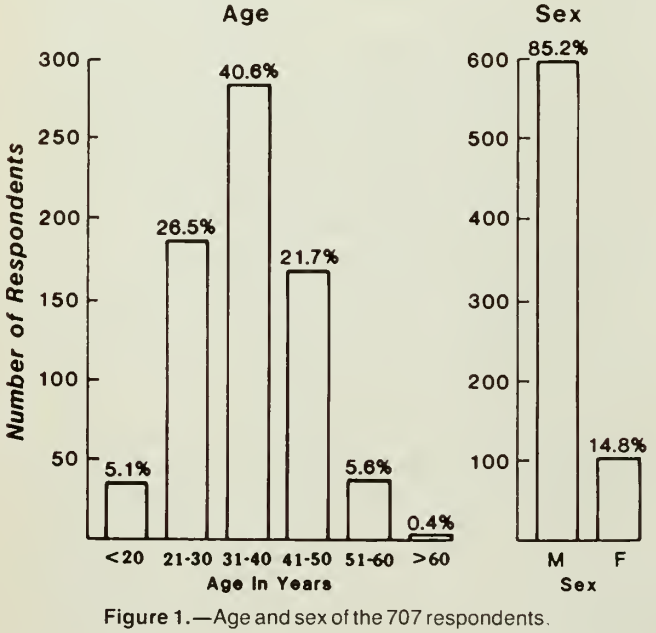

Figure 1.—Age and sex of the 707 respondents.

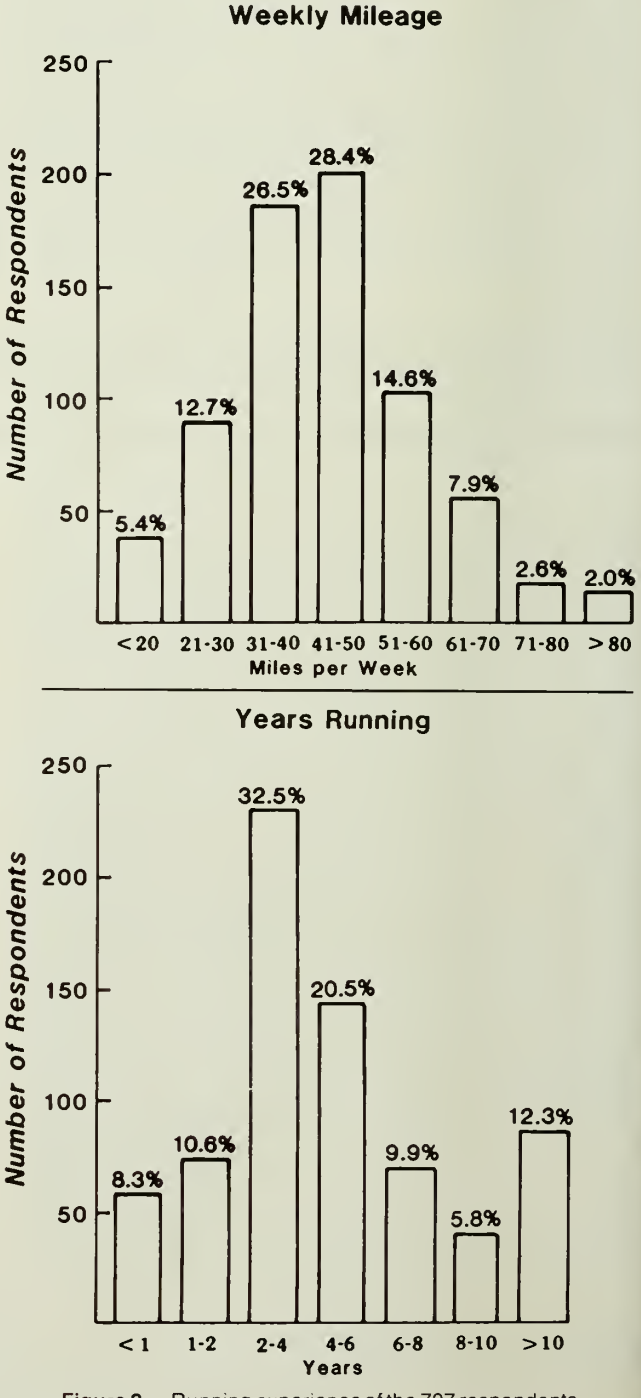

Figure 2.—Running experience of the 707 respondents.

TABLE 1.—*Frequency of Upper Gastrointestinal Tract Symptoms in 707 Marathon Runners*

Category	Symptom Present (Positive Response)* (% of total)		
	Heartburn	Nausea	Vomiting
A (easy run)	8.8	1.8	0.3
B (hard run)	9.5	11.6	1.8
C (after run)	3.5	12.7	1.8

*Symptoms were considered present (a positive response) when the respondent indicated "occasionally" or "frequently" and absent when "never" or "rarely" were checked. Percent of positive responses was calculated by dividing the sum of "occasionally" and "frequently" responses by the total number of responses.

TABLE 2.—*Frequency of Lower Gastrointestinal Symptoms in 707 Marathon Runners*

Category	Symptom Present (Positive Response)* (% of total)				
	Abdominal Cramps	Urge to have BM	Actual BM	Diarrhea	Bloody BM
A (easy run)	10.9	38.6	18.4	8.2	1.2
B (hard run)	19.3	36.4	16.0	10.0	1.8
C (after run)	13.9	38.2	34.9	19.2	2.4

BM = bowel movement

*Symptoms were considered present (a positive response) when the respondent indicated "occasionally" or "frequently" and absent when "never" or "rarely" were checked. Percent of positive responses was calculated by dividing the sum of "occasionally" and "frequently" responses by the total number of responses.

bowel movement. Each of these three symptoms was significantly more common after running, with 34.9% having a bowel movement, 19.2% having diarrhea and 2.4% having a bloody stool occasionally or frequently.

All lower GI tract symptoms were significantly more common in women in each of the three running categories (Figure 3). When analyzed by age groups, there was a trend for all lower GI tract symptoms in each of the three running categories to be more frequent in runners younger than 20 years (N=36) than ages 20 through 40 (N=467) or age older than 40 years (N=204) (Figure 4). This higher frequency of symptoms in young runners was statistically significant for "abdominal cramps" in all three categories, "diarrhea" during easy runs, and "urge to have a bowel movement" and "actual bowel movement" after running (Figure 4).

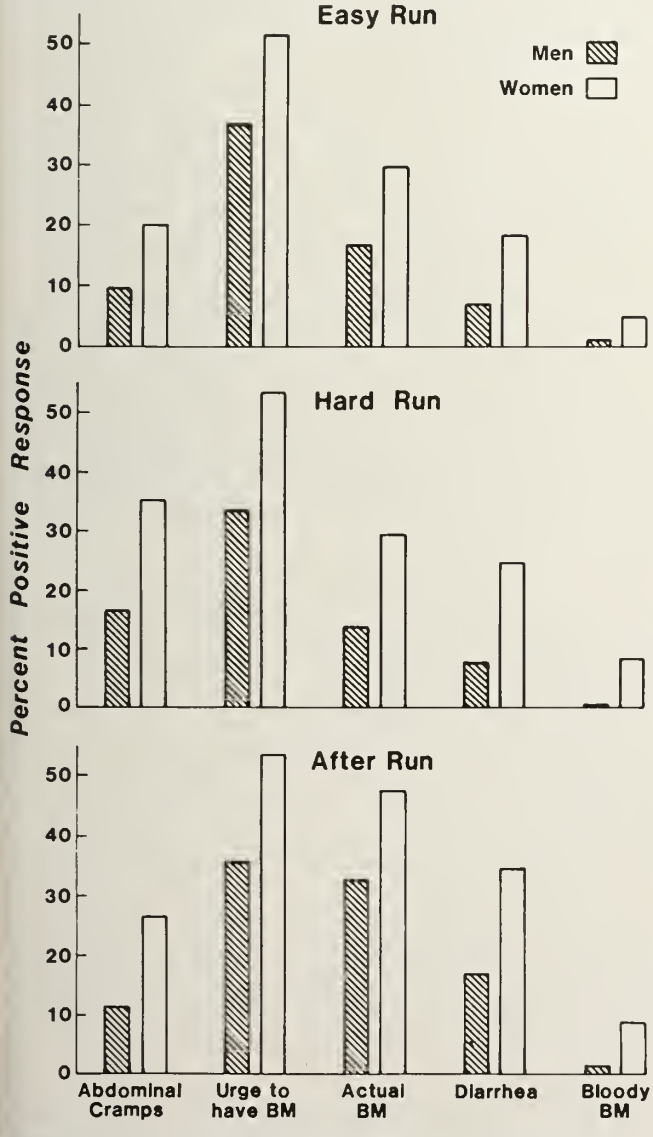

Figure 3.—Lower gastrointestinal tract symptoms in men and women. Bars represent the percent positive response (sum of "occasionally" and "frequently" responses divided by the total number of responses) for each sex. BM = bowel movement.

Anecdotal comments, while not subject to scientific analysis, provided additional information not directly requested in the questionnaire. Of the total respondents 131 (18.5%) volunteered comments, the majority addressing timing of eating and bowel evacuation before running and general dietary recommendations. Avoidance of food two to five hours before running was suggested by 26 respondents, and 23 persons felt that a bowel movement before running reduced GI disturbances. Dietary habits were considered important by 58 respondents, but there was no consensus and often items recommended by some—such as bran, fruit, beer—were felt best avoided by others. Some runners thought that conditioning lessened GI disturbances. Many persons found the onset of abdominal cramps and urgency to be predictable after running a certain distance (two, four or ten miles). Finally, eight persons were pleased that running was a "natural laxative" and alleviated their chronic constipation.

Discussion

This survey documents a high incidence of gastrointestinal tract symptoms in long-distance runners and confirms our anecdotal impressions. The following conclusions emerge from the data:

- Lower GI tract symptoms are more commonly associated with running than upper GI tract complaints.
- The urge to defecate is the most common symptom experienced by runners (36.4% to 38.6%) and appears both during and immediately after running.
- Bowel movements (34.9%) and diarrhea (19.2%) are relatively frequent immediately after running.
- Runners need to interrupt runs for bowel movements (16% to 18.4%) or diarrhea (8.2% to 10%) not infrequently.
- 1.2% to 2.4% of runners have bloody bowel movements associated with running.
- All lower GI tract symptoms are noted more commonly by women than by men.

- Some lower GI tract symptoms (abdominal cramps during and after running and urge to defecate or actual bowel movement after running) are more commonly experienced by younger than older runners.
- Heartburn occurs more commonly during than after running, whereas nausea (11.6% to 12.7%) and vomiting (1.8%) are more troublesome during hard runs or after running.

Although the results of our survey are striking, we recognize potential problems with the usage of questionnaires. The 41.6% response rate (707 persons) provided information from a relatively large number of runners, but respondents may be more likely to have had GI symptoms than nonrespondents. On the other hand, the large number of respondents should dilute this bias. Many of the GI disturbances surveyed in the Seaside marathon runners are characteristic symptoms of the irritable bowel syndrome,[6] and irritable bowel symptoms are reported in 13.6% to 17.1% of apparently healthy persons.[7,8] It would be of interest to compare GI symptoms experienced by runners during nonathletic stressful events with those experienced during running. Personality, diet or other selection factors may result in a higher incidence of the irritable bowel syndrome in runners than in nonrunners. Finally, the use of the same questionnaire in a control nonrunning population and a population participating in an alternative form of aerobic exercise might better define the relative significance of our survey results in runners.

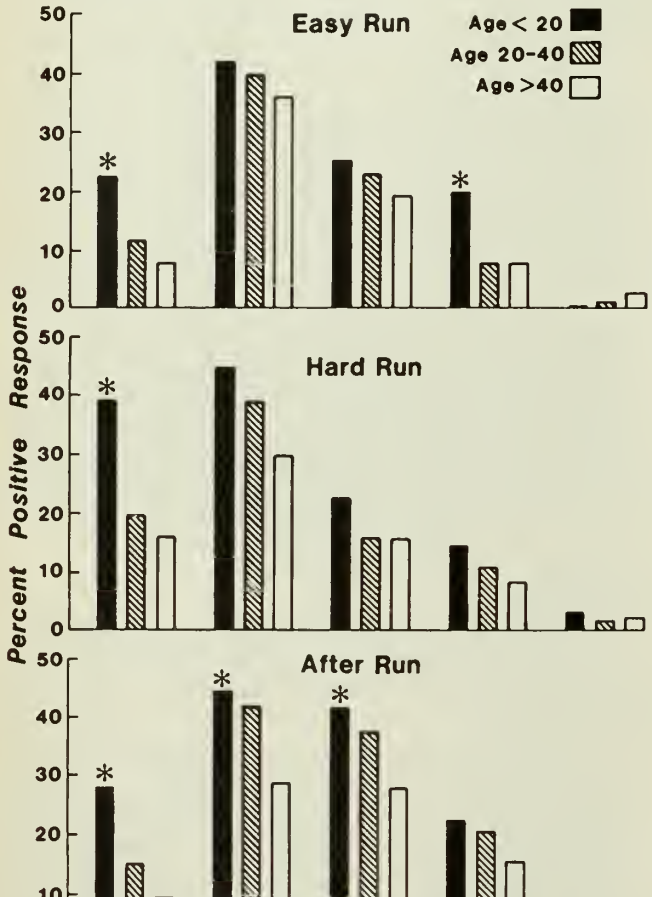

Figure 4.—Lower gastrointestinal tract symptoms in three age groups. Bars represent the percent positive response (sum of "occasionally" and "frequently" responses divided by the total number of responses) for age younger than 20, ages 20 through 40 and age older than 40 years. Asterisk (*) = statistically significant, comparing age younger than 20 with age older than 40 years. BM = bowel movement.

The pathophysiology of GI disturbances associated with running has not been studied and remains speculative. In spite of a resurgence of interest in physiologic investigations of marathon running, the GI tract has been neglected.[2] In one study subjects exercising on a treadmill had no differences in gastric emptying and intestinal absorption in comparison with baseline.[9] By contrast, in a more recent study it was noted that exercise on a bicycle ergometer accelerated gastric emptying but had no significant effect on small bowel transit time.[10] Increased serum gastrin has been associated with exercise.[11] Splanchnic, skin and renal blood flow are decreased during exercise while skeletal muscles receive a greatly increased percentage of cardiac output.[12] After a few minutes of continued exercise, intestinal arteries redilate by an "autoregulatory escape" mechanism, but mesenteric intestinal veins remain vasoconstricted.[13] The role of these circulatory changes in the GI symptoms of long-distance runners is unknown, but relative gut ischemia is often postulated as a likely explanation.[4] Gastrointestinal symptoms associated with running might also be explained by dietary factors, alterations in intestinal or colonic water and electrolyte fluxes, disturbances in GI motility or underlying irritable bowel syndrome. The physical pounding of running may induce physiologic events such as colonic mass movements that occur less often during other aerobic exercises such as cycling or swimming. The popularity of long-distance running and the frequency of GI disturbances documented by this survey invite future studies to explain these symptoms and to develop recommendations to reduce their occurrence.

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Use of β-Blockade and Hemoperfusion for Acute Theophylline Poisoning

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Five adults were treated successfully for severe theophylline poisoning due to intentional overdosage. Clinical features included nausea, tremor, delirium, hypotension and cardiac arrhythmias, metabolic acidosis, hyperglycemia, hypokalemia and hypophosphatemia. No seizures or deaths occurred despite very high serum theophylline concentrations (between 96 and 194 μg per ml). Extreme elevations of plasma catecholamines were documented and are implicated in the toxicity. β-Blockade with intravenous administration of propranolol hydrochloride was the most effective therapy for theophylline-induced hypotension. All patients were treated with resin hemoperfusion, which resulted in significant clinical improvement and rapid lowering of the serum theophylline level.

(Biberstein MP, Ziegler MG, Ward DM: Use of β-blockade and hemoperfusion for acute theophylline poisoning. West J Med 1984 Oct; 141:485-490)

Acute theophylline poisoning due to intentional or accidental ingestion of massive quantities of the drug has been reported with increasing frequency.[1-11] Complications include seizure, hypotension, cardiac arrhythmia and major metabolic disturbances. Mortality can be high.[1] Until recently, therapy has been largely limited to general supportive measures. During the past five years, hemoperfusion techniques have been applied to the treatment of theophylline poisoning.[2,4,6,7,9,12-14] We describe our recent experience treating five severely poisoned patients and outline an approach to acute theophylline poisoning. In addition, we propose that adrenergic hyperactivity contributes significantly to manifestations of theophylline poisoning and we present evidence of a therapeutic role for intravenous administration of propranolol hydrochloride in the treatment of severe theophylline-induced hypotension.

All patients herein described* had been given prescriptions for sustained-release theophylline preparations in conventional dosage weeks to months before admission. Compliance is unknown. Admissions were precipitated by a single deliberate ingestion of several grams of theophylline. In each case the clinical examination showed clear lung fields. Laboratory abnormalities that developed are shown in Table 1. Potassium and phosphate supplementation was given intravenously to all patients. Serum theophylline concentrations and measures intended to lower them are shown in Figure 1. All hemoperfusions were done using Amberlite XAD-4 resin cartridges (Extracorporeal Medical Specialists, King of Prussia, Pa). Vascular access was by femoral vein catheterization and blood flows of 200 ml per minute were achieved regularly. Heparin was given at a 4,000-unit loading dose followed by 2,000 units per hour by continuous infusion except where explicitly stated.

*We thank Dennis Leahy, MD; John Lilley, MD, and Robert Steiner, MD, for access to patients under their care.

Reports of Cases

CASE 1. The patient, a 61-year-old woman, said she attempted suicide two hours before admission by taking an overdose of a preparation of theophylline anhydrous, ephedrine hydrochloride and phenobarbital (TEP). She was alert with a blood pressure of 110/70 mm of mercury, pulse rate 120 per minute and respirations 28 per minute. The serum theophylline concentration was 88 μg per ml and the phenobarbital value was 3.8 mg per dl. A urine toxicology screen showed

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TABLE 1.—*Metabolic Abnormalities Observed in Five Theophylline-Poisoned Patients*

Case Number	Glucose mg/dl	Potassium mEq/liter	Phosphorus mg/dl	Creatine Kinase (%MM Isoenzyme) IU/liter	Arterial pH	PaO_2 mm Hg	$PaCO_2$ mm Hg
1	243	2.5	1.2	290(100.0)	7.36	108	28
2	349	1.7	0.7	363(98.1)	7.39	127	21
3	243	2.8	1.5	ND	7.34	77	33
4	439	1.8	0.8	4,932(98.0)	7.34	115	19
5	263	2.6	0.9	682(ND)	7.35	105	25

Pao_2 = partial arterial oxygen pressure, $Paco_2$ = partial arterial carbon dioxide pressure, ND = not determined

small amounts of acetaminophen, codeine, ephedrine, pseudoephedrine and diphenhydramine.

Over the subsequent two hours without therapy the patient became lethargic. Atrial fibrillation at a rate of 150 beats per minute developed and she had sustained hypotension with a systolic blood pressure of 60 mm of mercury. Volume challenge, cardioversion, digoxin, verapamil, procainamide hydrochloride, dopamine hydrochloride and Levophed (norepinephrine) bitartrate were tried in succession and had little effect on rate, rhythm or blood pressure. The serum theophylline concentration rose to 145 μg per ml (see Figure 1).

After four hours of sustained and severe hypotension at 60 mm of mercury systolic pressure, propranolol, 3.5 mg, was administered intravenously with a prompt rise in the blood pressure to 110/80 mm of mercury. Atrial fibrillation slowed to 110 beats per minute.

Over the next four hours the patient remained lethargic and confused. She was normotensive but atrial fibrillation persisted and the rate increased to 160 beats per minute. Hemoperfusion was done 22 hours after ingestion for two hours using a single resin cartridge. During the procedure, the serum theophylline value fell from 72 μg per ml to 38 μg per ml. Sinus rhythm resumed at 100 beats per minute. The platelet count after completion of the hemoperfusion was 210,000 per μl, the serum calcium level was 8.0 mg per dl and no complications occurred. The patient's subsequent hospital course was uneventful and she made a full recovery.

Case 2. The patient, a 15-year-old girl with asthma who weighed 55 kg, took about 12 grams of the sustained-release anhydrous theophylline preparation, Theo-Dur. Ninety minutes later, induced emesis yielded pill fragments. Activated charcoal and magnesium citrate were given. The serum theophylline concentration was 44 μg per ml and rose progressively over the ensuing six hours to 134 μg per ml (see Figure 1). The patient was transferred to University of California Medical Center, San Diego, where she was found to be confused, hyperirritable and combative. She complained of nausea. There was a continuous generalized tremor that resembled shivering. Her blood pressure was 110/20 mm of mercury, pulse rate 150 per minute and regular and respirations 28. Her hematocrit was 42%. There was no ketonemia. A moderate amount of ephedrine was found in a urine specimen. Additional doses of activated charcoal and cathartic were given with resultant appearance of visible charcoal in a stool specimen.

An hour after admission, hemoperfusion was initiated. Physical restraint and 5 mg of diazepam given intravenously were required to subdue the patient enough to allow initiation of the treatment. After 40 minutes a blood flow of 220 ml per minute was achieved and sampling of blood from inlet and outflow sides of the resin cartridge showed serum theophylline concentrations of 132 μg per ml and 2 μg per ml, giving a hemoperfusion cartridge clearance of 2.3 ml a minute per kg.[2,15] Repeat inlet and outflow values after two hours of hemoperfusion were 70 μg per ml and 40 μg per ml, respectively. The cartridge was replaced at three hours, at which time inlet and outflow theophylline values were 55 μg per ml and 54 μg per ml, indicating saturation of the cartridge. Treatment was continued

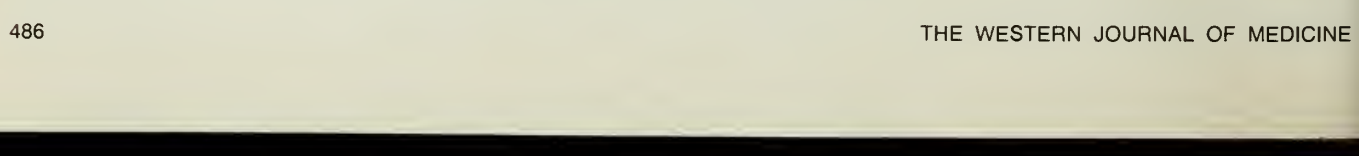

Figure 1.—Serum theophylline levels in cases 1 through 5. The shaded blocks indicate hemoperfusion treatments and the arrows denote oral administration of activated charcoal and magnesium citrate.

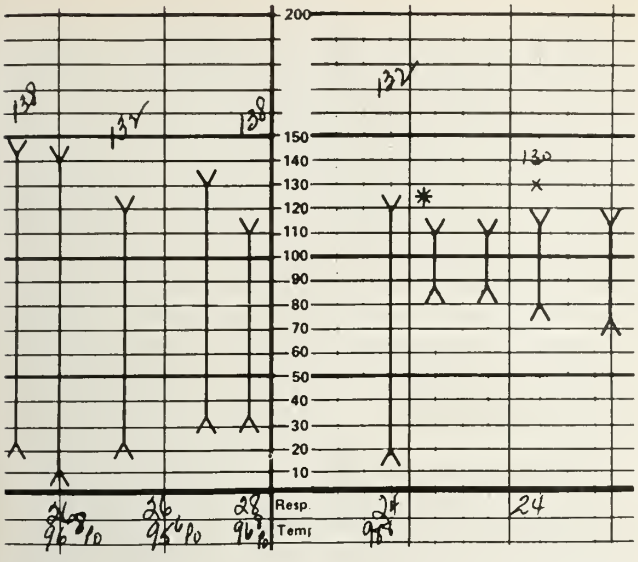

Figure 2.—Intensive care unit record of case 2. Pulse rate is written at the top. Systolic (V) and diastolic (Λ) blood pressures are shown. Vertical lines are at hourly intervals. The asterisk marks the point of intravenous administration of 2 mg of propranolol. The response suggests restoration of normal peripheral vascular resistance.

for 2½ hours more using a second cartridge. The serum theophylline concentration fell progressively during the treatment from 175 μg per ml to 29 μg per ml (see Figure 1). A platelet count immediately following the procedure was 229,000 per μl and the serum calcium level was 8.8 mg per dl.

The clinical response to therapy was dramatic. Within two hours of initiation of hemoperfusion, the patient was alert and cooperative. Because of continued tremor and tachycardia and because of the previous favorable response, propranolol, 2 mg, was administered intravenously. The tremor and tachycardia responded minimally but her blood pressure rose dramatically from 110/20 to 110/80 mm of mercury (see Figure 2). The patient's subsequent course was uneventful and she was discharged three days later.

The amount of theophylline bound by the first resin cartridge used was subsequently measured.* An aliquot of the mixed and washed resin was analyzed by repeated elution with a mixture of ethyl acetate, dichloromethane and isopropanol. The eluate was evaporated to dryness and the residual powder was resuspended in drug-free serum. The theophylline concentration was then measured in a standard enzyme-linked immunoassay. By calculation this resin cartridge contained 1.26 grams of theophylline, assuming complete elution.

Case 3. The patient, a 50-year-old woman with schizophrenia and chronic obstructive pulmonary disease, claimed to have ingested 30 grams of Theo-Dur in a suicide attempt. She had symptoms of nausea and generalized discomfort. She was agitated and tremulous. Her blood pressure was 110/60 mm of mercury, pulse was regular at 180 beats per minute and respirations were 40. She received ipecac and vomited. Activated charcoal and magnesium citrate solution were given but no bowel movement occurred. Fourteen hours after ingestion, her serum theophylline concentration was 132 μg per ml (see Figure 1) and her condition had not improved. She then received 100 grams of activated charcoal and 300 ml of magnesium citrate solution every hour for three consecutive hours. Hemoperfusion was begun 17 hours after ingestion. The patient soon felt less nauseated and her tremor ceased. Her pulse rate slowed to 110 beats per minute with a stable blood pressure of 110/70 mm of mercury. At the end of the procedure, a platelet count was 189,000 per μl and serum calcium level was 8.3 mg per dl. The serum theophylline concentration fell from 68 μg per ml to 16 μg per ml (see Figure 1). The patient did well except for the development of a moderate groin, which was treated with local pressure and two units of transfused packed red cells.

The plasma epinephrine level was 326 pg per ml (normal, recumbent, 0 to 80 pg per ml) and norepinephrine level was 3,200 pg per ml (normal, recumhematoma at the vascular catheter site in the right bent, 150 to 550 pg per ml) before hemoperfusion. Radioenzymatic assay of blood from arterial and venous limbs of the hemoperfusion cartridge showed that catecholamines were not cleared by resin hemoperfusion.

Case 4. This 33-year-old woman with a history of bronchitis and depression ingested 12 grams of the sustained-release theophylline preparation, Slo-Phyllin. An hour later she was agitated, diaphoretic, tremulous, nauseated and vomiting. Her blood pressure was 90/50 mm of mercury, pulse was 160 per minute and respirations were 40. A serum theophylline concentration was 70 μg per ml. A solution of activated charcoal and magnesium citrate was administered but no bowel movement occurred. Her agitation increased. Her systolic blood pressure fell to 60 mm of mercury and was refractory to fluid challenge and administration of dopamine. Atrial fibrillation developed and she had two episodes of ventricular tachycardia requiring cardioversion. Arrhythmias were refractory to administration of lidocaine hydrochloride. After eight hours in hospital, hemoperfusion was initiated. Full neuromuscular paralysis with pancuronium bromide was required. Two resin cartridges clotted. A third cartridge remained patent with 10,000 units per hour of heparin given intravenously, but gross hematuria and a bloody nasogastric aspirate developed, and the patient was transfused with four units of packed erythrocytes. Her platelet count fell from 277,000 per μl to 82,000 per μl. A serum calcium level was 8.0 mg per dl after hemoperfusion. Four hours of hemoperfusion resulted in dramatic clinical improvement and a fall in the serum theophylline value from 194 μg per ml to 48 μg per ml (see Figure 1). Her blood pressure rose to 120/90 mm of mercury and arrhythmias ceased. She was discharged four days later.

A plasma epinephrine level was 638 pg per ml and

*David Bailey, MD, quantitated the theophylline bound to a resin column.

norepinephrine was 5,966 pg per ml before hemoperfusion. A plasma insulin level by radioimmunoassay was 279 μU per ml (normal fasting, 4 to 24 μU per ml).

CASE 5. The patient, a 24-year-old man with schizophrenia, came into the emergency room eight hours after having taken 6 grams of Theo-Dur in an attempt, he said, to improve his breathing. He had nausea, vomiting and abdominal pain and was anxious, hyperirritable and tremulous. His blood pressure was recorded as 140/0 mm of mercury, pulse rate 120 per minute and respirations 36. The serum theophylline concentration was 90 μg per ml. Serum lactate level was 80 mg per dl. The patient was given multiple doses of activated charcoal and magnesium citrate by nasogastric tube (Figure 1). Diazepam was given to control agitation and combativeness. Hemoperfusion was initiated four hours after admission but two cartridges clotted. It was successful using a third cartridge and giving 4,000 units per hour of heparin by continuous infusion. His tremor, agitation and tachycardia abated. The serum theophylline value fell from 96 to 35 μg per ml (see Figure 1). At the end of the procedure, the serum calcium level was 9.8 mg per dl but the platelet count had fallen from 283,000 per μl to 19,000 per μl. A partial thromboplastin time was greater than 200 seconds. A femoral artery blood specimen drawn 30 minutes after the completion of hemoperfusion resulted in a large hematoma requiring transfusion of two units of packed erythrocytes. The patient recovered fully from the ingestion. Psychiatric consultants found him to be psychotic and actively suicidal.

Discussion

Theophylline intoxication is a common problem that occurs in two distinct clinical settings. In patients who have been repeatedly administered standard doses of the drug, subacute or chronic intoxication may develop that is often attributable to excessive dosage or decreased clearance due to heart failure, liver disease or drug interactions.[16-18] Such patients may have serious complications such as seizure at blood concentrations that are just above the therapeutic range.[17] In contrast we and others[1-11] report a syndrome of acute massive ingestion in which very high blood levels may be initially well tolerated but that may nonetheless have a fatal outcome. This distinction is critical in interpreting serum theophylline concentrations and also in formulating criteria for aggressive therapeutic intervention. In Table 2 findings from the present series are compared with those from two previously published series of adults with acute theophylline poisoning.

The standard treatment of theophylline poisoning includes emptying the stomach and monitoring closely for cardiovascular and neurologic complications. In addition, administering activated charcoal and an osmotic cathartic to limit absorption is important especially when dealing with sustained-released theophylline preparations.[19] Furthermore, it has been shown that repeated oral dosing with activated charcoal increases the rate of elimination of theophylline from the blood.[20] In case 3, repeated hourly administration of charcoal and magnesium citrate until charcoal was seen in the stool resulted in a remarkable fall in the serum theophylline value to 70 μg per ml that occurred before the initiation of hemoperfusion (Figure 1).

Theophylline administration has recently been shown to stimulate catecholamine release.[21-24] Our finding of very high plasma levels of epinephrine and norepinephrine in cases of acute theophylline poisoning is therefore not altogether unexpected and very likely represents a direct pharmacologic effect of the drug rather than simply a stress reaction. The effects of these high catecholamine levels on β-adrenergically mediated functions may be magnified by theophylline-induced intracellular phosphodiesterase inhibition, which is likely to be substantial at the extreme theophylline levels found in acutely poisoned patients. We therefore propose that acute theophylline poisoning produces a state of uncontrolled β-adrenergic stimulation that accounts at least in part for many of the toxic effects, including cardiac arrhythmias, hypotension, tremor, agitation and metabolic disturbances. This provides a rationale for therapeutic intervention with β-blocking agents.

Metabolic disturbances in cases of acute theophylline poisoning have been reported previously and include hyperglycemia,[3,7,8,10,25] hypokalemia[1,5-8,10,25] and metabolic acidosis[4-6,8,25] probably due to lactate accumulation (case 5).[25] These abnormalities were present in all of our cases (see Table 1). In addition, we report the consistent development of severe hypophosphatemia, a metabolic abnormality previously documented in only a single case of mixed overdosage with theophylline and a sympathomimetic.[25] The creatine kinase levels were also uniformly mildly raised, ascribable to abnormal muscular activity or hypophosphatemia (or both). The hypothesis that these metabolic abnormalities are due to adrenergic overdrive has now been confirmed by the work of our colleagues, Dr T.

TABLE 2.—*Three Studies of Acute Theophylline Poisoning in Adults**

Study	*Number of Patients*	*Peak Theophylline Concentrations μg/ml Mean*	*Range*	*Patients Hemoperfused*	*Outcome*
Helliwell and Berry, 1979[1]	8	68	25-120	0	2 deaths
Park et al, 1983[2]	5	80	71-90†	4 (charcoal)	1 with severe residual neurologic deficits
This study	5	148	96-194	5 (Amberlite XAD-4)	All recovered

*Pediatric and nonacute cases are excluded.
†Denotes values obtained by extrapolation. Other peak levels represent highest values directly measured.

Kearney and Dr G. Curtis at this institution (oral communication, October 1983). They have found that in theophylline-poisoned dogs pretreatment with propranolol prevented hyperglycemia, hypokalemia, hypophosphatemia and acidosis. However, propranolol administration after these metabolic abnormalities were established was much less efficacious. Whether propranolol has a place in the prevention or treatment of these metabolic abnormalities in theophylline-poisoned patients remains to be explored. For now, we prefer the safety, rapidity and reliability of intravenous supplementation of potassium and phosphate, even though total body stores are probably normal. Severe acidemia can be treated by giving sodium bicarbonate intravenously. Insulin therapy appears inappropriate because the hyperglycemia is transitory and well tolerated, because there is a risk of exacerbation of hypokalemia and hypophosphatemia and because endogenous insulin production where measured appears fully intact (case 4).[25]

Hypotension is a common though poorly understood complication of massive theophylline ingestion.[1,4-6,8,10] It is frequently refractory to conventional vasopressors (cases 1 and 4) and contributes significantly to mortality.[1] Strubelt and co-workers[26] showed that theophylline-induced hypotension in rats could be greatly attenuated by concomitant parenteral administration of propranolol. Kearney and Curtis (oral communication, October 1983) have had similar results in dogs. To our knowledge, cases 1 and 2 provide the first evidence of the efficacy of propranolol in treating hypotension in humans who have theophylline poisoning, though we have been told recently of a third such case in which the patient's blood pressure rose from 80/0 to 110/80 mm of mercury when given propranolol intravenously.

In case 1 the slowing of rapid atrial fibrillation by propranolol probably contributed to the rise in the blood pressure. However, it is clear from case 2 that other factors are also involved. In case 2 (see Figure 2) a substantial rise in mean arterial pressure occurred in the absence of a change in heart rate, suggesting that theophylline poisoning causes a severe impairment of normal peripheral vasomotor tone that is reversible with propranolol given intravenously. Theophylline does in fact have vasodilatory properties[16,27] and the intravenous administration of propranolol, by blocking β_2-receptors on vascular smooth muscle, may increase peripheral vascular resistance.[28,29] One could further hypothesize that the pathogenesis of theophylline-induced hypotension involves accumulation of adenosine 3′:5′-cyclic phosphate (cyclic AMP) within vascular smooth muscle cells due to the synergistic effects of β-adrenergic hyperactivity and phosphodiesterase inhibition. Cyclic AMP would then mediate vascular smooth muscle relaxation by mechanisms well described elsewhere.[30]

It is not surprising that conventional sympathomimetic vasopressors may be quite ineffective as in cases 1 and 4. One might even expect an exacerbation of hypotension from drugs such as dopamine that at certain doses have primarily β-specificity. Furthermore, these sympathomimetic drugs can aggravate many toxic effects of theophylline including cardiac arrhythmias. In contrast, propranolol not only alleviates hypotension but may also alleviate theophylline-induced arrhythmias, tremor, agitation and metabolic derangements. Moreover, it blocks the effects of many sympathomimetic drugs that are prescribed along with theophylline for treatment of bronchospasm and that are often ingested with theophylline (cases 1 and 2). The use of β-blockade could be questioned in patients who have asthma, but we have encountered no bronchospasm in the setting of acute theophylline poisoning either before or after propranolol administration. Clearly, judgment must be exercised. Nevertheless, we feel that giving propranolol intravenously can be very useful in treating theophylline-induced hypotension.

Once seizures have occurred, the outcome in cases of both acute and chronic theophylline poisoning is often poor, regardless of the therapy used.[1,2,4,8,12] For this reason there has been considerable interest in using hemoperfusion to remove the drug before seizures have occurred. Because seizures have been reported in cases of acute poisoning with concentrations as low as 85 and 90 μg per ml,[1,2] we recommend that hemoperfusion be considered for acutely poisoned patients with concentrations above 60 μg per ml, especially if the levels are still rising. Similar recommendations have been made by others.[2,31] This approach applied in cases 2, 4 and 5 resulted in rapid lowering of serum theophylline values and significant clinical improvement and possibly prevented seizures. In cases 1 and 3, hemoperfusion was instituted late, at a time when levels were, unbeknown to the physicians involved, already declining and results were less impressive. Earlier intervention in case 1 might have prevented life-threatening arrhythmia and hypotension. Criteria for initiation of hemoperfusion in cases of more subacute to chronic intoxication are more difficult to formulate. Life-threatening complications occur at lower serum concentrations[17] and experience in this setting is limited. Of four reported cases one patient died.[2,12-14]

The extraction of theophylline from Amberlite resin after hemoperfusion has not been previously reported. The amount extracted, 1.26 grams, is relatively small compared with the maximum possible total body burden of 4.81 grams calculated as 175 mg per liter (peak serum level × 55 kg (body weight) × 0.5 liters per kg (volume distribution of theophylline).[16] Three points should be made, however. First, though exhaustive elutions were done, the extraction from the resin may nonetheless have been incomplete. Second, another column was used for two hours after the first so that a reasonable estimate of the total amount removed by hemoperfusion might approach 2 grams. Third, the amount of theophylline removal required to prevent life-threatening complications is not known but may be of this magnitude.

Bleeding is a known risk of hemoperfusion but is

said to occur uncommonly.[32,33] In the present series bleeding complications developed in three of five patients. Contributing factors included platelet depletion (cases 4 and 5), the need for larger than usual doses of heparin (cases 4 and 5), an unnecessary arterial puncture (case 5) and early removal of a femoral vascular catheter in a patient who still showed substantial heparin effect (case 3). We feel that although none of the patients suffered serious morbidity as a result of bleeding, the potential definitely exists. We currently place emphasis on careful monitoring of vital signs, hemoglobin and platelet count and on avoiding the aforementioned errors.

In summary, we believe that most patients with acute theophylline intoxication can be managed in a traditional manner including careful monitoring, intensive support and thorough evacuation of remaining drug from the gastrointestinal tract. Repeated doses of charcoal and an osmotic cathartic should be administered at least until charcoal is visible in the stool. Metabolic abnormalities including hyperglycemia, hypokalemia, hypophosphatemia and acid-base disturbances should be expected and treated as discussed. Intravenous administration of propranolol may be useful, especially for refractory theophylline-induced hypotension. Finally, there is a subset of acutely poisoned patients with life-threatening complications or serum levels above 60 μg per ml and still rising who should be considered for hemoperfusion, a procedure that has the capacity to remove significant quantities of theophylline, which can result in dramatic clinical improvement.

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Medical Progress

Magnetic Resonance Imaging Part I—Physical Principles

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Magnetic resonance (MR) imaging is the most complex imaging technology available to clinicians. Whereas most imaging technologies depict differences in one, or occasionally two, tissue characteristics, MR imaging has five tissue variables—spin density, T_1 and T_2 relaxation times and flow and spectral shifts—from which to construct its images. These variables can be combined in various ways by selecting pulse sequences and pulse times to emphasize any desired combination of tissue characteristics in the image. This selection is determined by the user of the MR system before imaging data are collected. If the selection is not optimal, the imaging process must be repeated at a cost of time and resources.

The optimal selection of MR imaging procedures and the proper interpretation of the resultant images require a thorough understanding of the basic principles of MR imaging. Included in this understanding should be at least the rudiments of how an MR imaging signal is produced and why it decays with time; the significance of relaxation constants; the principles of scanning methods such as saturation recovery, inversion recovery and spin echo; how data obtained by these methods are used to form an image, and how the imaging data are compiled by multi-slice and volumetric processes. In selecting an MR imaging unit, information about different magnet designs (resistive, superconductive and permanent) is useful. Although no bioeffects are thought to be associated with an MR imaging examination, some knowledge of the attempts to identify bioeffects is helpful in alleviating concern in patients.

Clinical applications of magnetic resonance imaging will be discussed in a subsequent issue.

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With the classical experiment of Stern and Gerlach[1,2] on the deflection of atomic beams in a magnetic field as a foundation, Rabi[3] identified the role of nuclear magnetism on the magnitude of deflection. For this work he was awarded the Nobel prize in physics in 1944. Evolution of these early results into the analytic tool of nuclear magnetic resonance (NMR) was pioneered principally by Bloch[4] and Purcell,[5] who shared the Nobel prize in 1952. These persons recognized that certain nuclei will resonate and emit a radio signal if they are placed in a strong magnetic field and pulsed with radiofrequency energy. Analysis of the amplitude and frequency distribution of the emitted signal yields information about the chemical composition of the sample containing the nuclei. This analysis is the principle of NMR spectroscopy, an analytic technique of considerable value, initially in chemistry and later in biochemistry and animal physiology.

In 1971, Damadian[6] suggested that one of the NMR variables, the spin-lattice relaxation time, was different for benign and malignant tissue of the same origin, and that this difference might be useful in distinguishing between the two tissues. Two years later, Lauterbur[7] proposed a method of producing images by NMR. Although the first NMR images produced in the mid-1970s were not very impressive (Figure 1), the technology evolved rapidly and today magnetic resonance (MR) imaging is perhaps the most exciting development in the entire field of medical imaging.

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This is Part I of a two-part article. Part II will appear in a subsequent issue.

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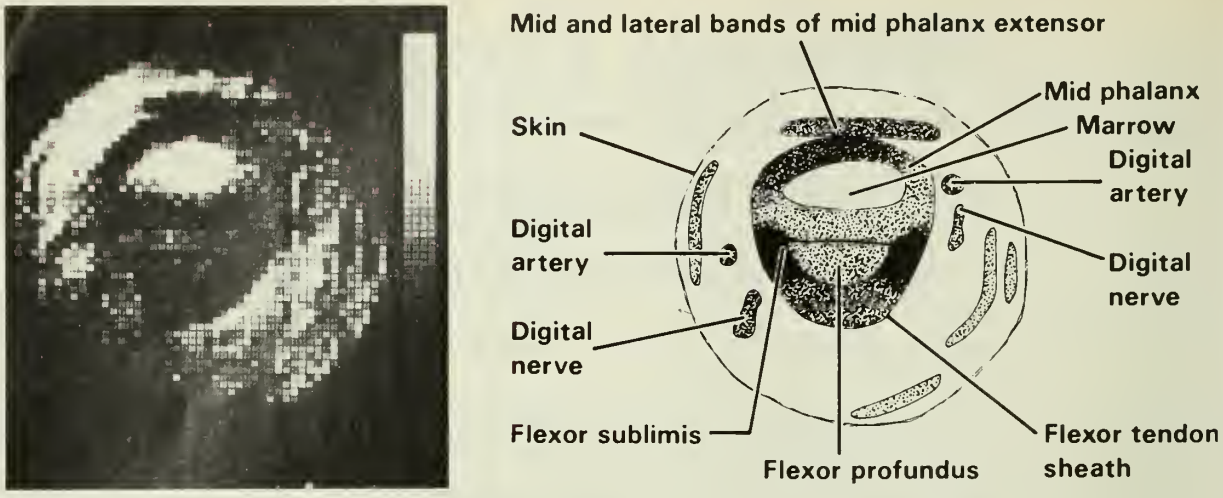

Figure 1.—A magnetic resonance (MR) image of a finger obtained in vivo in 1976. This is the first human MR image that showed significant soft tissue details (from Mansfield & Maudsley[8]).

ABBREVIATIONS USED IN TEXT

CT = computed tomography
FDA = Food and Drug Administration
MR = magnetic resonance
NMR = nuclear magnetic resonance
T_1 = spin-lattice relaxation time
T_2 = spin-spin relaxation time
2DFT = two-dimensional Fourier transformation
TR = pulse repetition time

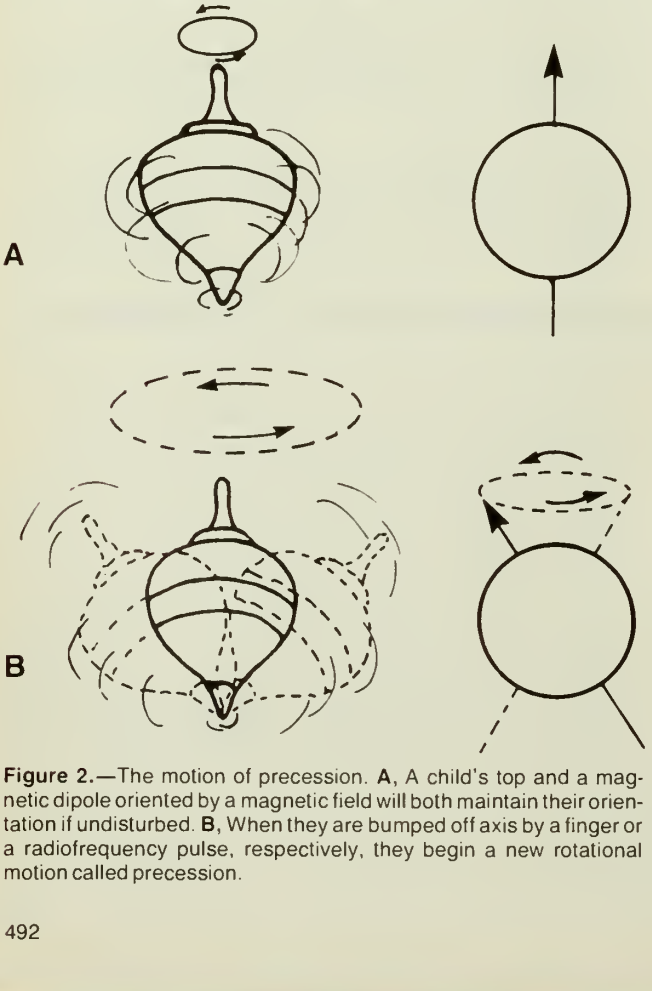

Figure 2.—The motion of precession. **A**, A child's top and a magnetic dipole oriented by a magnetic field will both maintain their orientation if undisturbed. **B**, When they are bumped off axis by a finger or a radiofrequency pulse, respectively, they begin a new rotational motion called precession.

Obtaining an MR Imaging Signal

In the nucleus, each neutron and proton spins on its axis, yielding a magnetic moment that causes the particle to behave like a small magnet. In most nuclei, the neutrons and protons align so that their spins and magnetizations cancel. Complete cancellation is not possible, however, if the number of protons or neutrons is odd. In hydrogen, for example, the nucleus contains a solitary proton. This proton generates a small magnetic field, represented by a vector along the axis of spin. In a substance with nuclei containing one or more unpaired protons or neutrons, the dipoles are oriented randomly so that the substance possesses no net magnetization. When a magnetic field is applied to the substance, however, the dipoles become oriented with respect to the magnetic field. This new orientation induces a net magnetization—termed the magnetic moment—in the sample.

With such a magnetized sample, application of a low energy pulse of the proper frequency will cause the sample to absorb some of the energy and to tilt the sample's magnetic moment out of alignment with the field. In the tilted orientation, the magnetic moment begins a motion called precession, in which it rotates slowly in a motion that describes the wall of a cone (Figure 2). This rotation causes the emission of a radio signal from the sample. The frequency of this signal is identical to the precessional frequency and is termed the Larmor frequency (ν). The Larmor frequency is the product of the magnetic field strength (B) and the gyromagnetic ratio (γ) of the nuclei in the sample:

$$\nu = \gamma B$$

The Larmor frequency is unique for each type of nucleus; in a given magnetic field, therefore, all identical nuclei, such as in hydrogen, emit a signal of the same frequency. The frequency of this signal varies only with the magnetic field strength. This feature is important in encoding the signal with spatial information in the process of forming a magnetic resonance image.

Decay of the NMR Signal

When the magnetic moment of a sample is pulsed out of alignment with the applied field, its precessional motion

tends to reorient into alignment with the field. This realignment process is termed spin-lattice relaxation. At the same time, the precessing magnetic moment tends to break apart through a dephasing process termed spin-spin relaxation. Both relaxation processes contribute to decay of the radio signal emitted from the sample. It is important to understand these processes because they determine the appearance of various tissues in a magnetic resonance image.

Relaxation processes can be explained simply by a conceptual scheme called the rotating frame of reference. With this scheme, precession is represented by a single stationary vector in the zy plane of a three-dimensional coordinate system (Figure 3A). The central angle of the cone of precession (θ) corresponds to the angle between the magnetization vector and the applied magnetic field.

Spin-lattice relaxation involves the gradual return of the magnetic moment of a sample into alignment with the applied magnetic field. As the angle θ decreases, the intensity of the emitted radio signal decreases (Figure 3B), until eventually the sample's magnetic moment is once again aligned with the applied field (Figure 3C). The rate at which the magnetization (M) decays with time (t) is described mathematically as

$$M = M_0(1\text{-}e^{-t}/T_1)$$

in which T_1 is the spin-lattice relaxation time and M_0 is the original magnetization. Different substances have different T_1 values, signifying that spin-lattice relaxation occurs at different rates in different substances as a reflection of the interaction of the precessing magnetic moment with the sample as a whole. The signal in a substance with short T_1 decays faster than that from a substance with long T_1.

Spin-spin relaxation occurs by a different mechanism (Figure 4). The precession of the tilted magnetic moment is influenced by small inhomogeneities in the surrounding magnetic field. These inhomogeneities cause the precessing magnetic moment to separate or dephase into components, leading to a loss in signal intensity. This dephasing process is termed spin-spin relaxation, T_2.

Spin-spin relaxation in a rotating reference frame is depicted in Figure 4. In Figure 4A, the magnetic moment of the sample is aligned with the applied magnetic field. In Figure 4B, the magnetic moment is tilted out of alignment by a radiofrequency pulse, and the magnetic moment begins to precess about the applied field. In Figure 4C, localized inhomogeneities in the applied field cause the precessing mag-

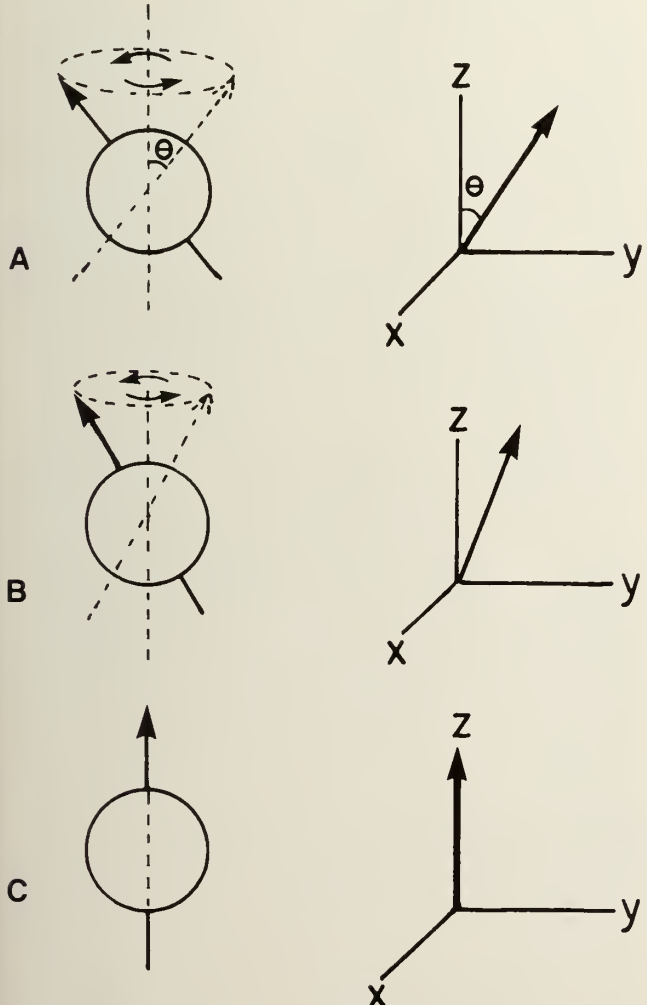

Figure 3.—Spin-lattice relaxation diagrammed in the rotating frame of reference. The precession of the magnetic moment of a sample is represented by a cone swept out by the magnetization vector in a standard coordinate system, or by a single, stationary vector at an angle with the applied field in a rotating frame of reference (**A**). As the magnetic moment reorients towards the applied field by spin-lattice relaxation (T_1), θ decreases (**B**). Eventually, the magnetic moment of the sample once again lies along the z axis in the direction of the applied field (**C**).

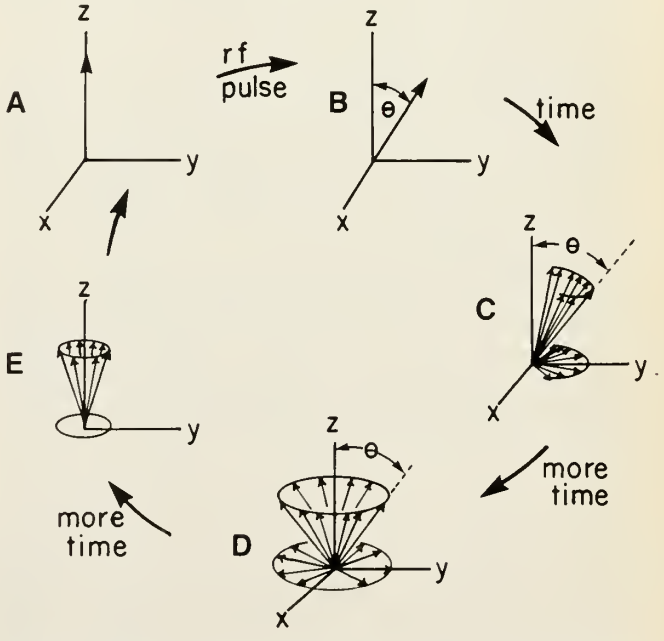

Figure 4.—Spin-spin relaxation diagrammed in the rotating frame of reference (**A**). Immediately following a radiofrequency (rf) pulse, the magnetic moment of the sample can be represented by a single vector (**B**). As the magnetization vector begins to break up or to dephase due to localized nonuniformities in the applied field, components of the vector begin to fan-out in the xy plane (**C**). When there are an equal number of components in all directions in the xy plane, the components cancel one another and the magnetic resonance imaging signal disappears (**D**). As time passes, the cone representing the precessing but dephased magnetic moment continues to narrow because of spin-lattice relaxation (**E**) until the magnetic moment once again is realigned with the applied field (**A**) (from Pykett[9]).

netic moment to separate into various components precessing at slightly different frequencies. This dephasing process, termed spin-spin relaxation T_2, leads to a decay in signal intensity characterized by the expression

$$I = I_0 e^{-t/T_2}.$$

When the dephasing process is complete (Figure 4D), each xy component of the signal is balanced by a component in the opposite direction, and the signal intensity falls to zero. Still, the magnetization vector continues to realign with the applied field (Figure 4E) until realignment is complete (Figure 4A).

Spin-spin relaxation and spin-lattice relaxation are separate processes caused by different interactive mechanisms. Variations in molecular structure or chemical composition produce changes in the rates of each type of relaxation, reflected by differences in T_1 and T_2. The only generalization possible is that T_2 can approach, but never exceed, T_1.

Variations in Relaxation Constants

Three variables influence the strength of the proton NMR signals. These variables are the concentration of protons and the relaxation constants T_1 and T_2. In most tissues, the concentration of protons is related principally to the water content and secondarily to the lipid content. Water concentrations vary by only 15% or so from one tissue to another. Images that reflect only proton density (also called "spin density") do not have as much contrast as many images that also reflect T_1 and T_2 differences. Still, proton density images have superior gray-white matter differentiation compared with computed tomography (CT).

Spin-lattice relaxation occurs with the help of thermal motion in the sample. As thermal motion increases, energy transfer processes also increase and relaxation by spin-lattice interactions occurs more readily. Because temperature is a measure of thermal motion, increasing the temperature of a sample leads to a reduction in T_1.

T_1 varies from one tissue to another, depending in part on whether it is more "solidlike" or more "liquidlike."[10] In solids, the atoms are held rigidly in place by interatomic bonds and they rarely collide with each other. This rigidity leads to relatively long spin-lattice relaxation times, with T_1 values often on the order of many seconds or more. Most biologic tissues are more liquidlike in their T_1 behavior; for example, most water in tissue is in a relatively unbound condition and the molecules move and collide frequently. These molecules provide "thermal contact" in the interstices of tissues and accelerate the process of spin-lattice relaxation.[10] Hence, T_1 values for most soft tissues are measured in milliseconds—that is, soft tissues have T_1 values of 300 to 700 ms at the magnetic field strengths currently used for imaging.

Spin-spin relaxation T_2 depends on the interaction of the magnetization vector with localized nonuniformities in the applied field. In a solid, the atoms are relatively fixed in space and the interactions giving rise to T_2 tend to reinforce the decay process over time. In a liquid, the molecular motion leads to slight changes in the distribution of magnetic nonuniformities with time, prolonging the values of T_2. Many disease processes increase the water content of solid tissues, and thereby increase their T_2 values (Table 1).

TABLE 1.—*Effects of Various Disease Processes on Proton ("Spin") Density and Relaxation Constants T_1 and T_2*

Disease Process	*Spin Density*	*T_1*	*T_2*
Cerebral infarction	↑	↑	↑
Hemorrhage	↑	↑	↓
Edema	↑	↑	↑
Multiple sclerosis	↑	—	↑
Malignant tumor	↑	—	↑
Pituitary tumor	—	↑	—
Cyst	—	↑↑	↑

↑ = increased, ↓ = decreased

Scanning Methods

Pure spin density—that is, proton density—images have limited usefulness. Furthermore, the relaxation times T_1 and T_2 are difficult to measure exactly. Consequently, methods that use various combinations of proton density, T_1 and T_2 are used most frequently in clinical imaging.

At least eight different imaging methods have been reported. However, the three most widely used are variants of the family of pulse techniques. All pulse-imaging methods begin with the magnetization vector aligned with the magnetic field along the z axis. Then a radiofrequency pulse is applied to orient the vector away from the z axis and to induce precession. At a slightly later time, the first radiofrequency pulse is followed by one or more additional pulses applied before relaxation is complete. Each imaging method uses a different combination of the first and succeeding pulses and of the time interval between them. These combinations yield images that emphasize one particular component of the tissue characteristics accessible to MR imaging (spin density, T_1 or T_2).

The imaging method termed saturation recovery (often referred to as partial saturation) consists of a series of equally spaced pulses, each of which rotates the magnetization vector through 90 degrees (Figure 5). Immediately following the first pulse, the magnetization vector lies in the xy plane and furnishes a maximum MR imaging signal. Spin-lattice and spin-spin relaxation then begins and the magnetization vector starts to relax toward the applied field (z axis) at different rates in different regions of the sample, according to the T_1 value of each region. Then, additional 90-degree pulses are applied and the signal is measured immediately after each. The interval between successive pulses is referred to as the pulse repetition time (TR). The second pulse causes the magnetization vector to rotate through another 90-degree arc; this time, however, the vector goes beyond the xy plane by an amount determined by the degree of relaxation occurring between pulses. In regions of tissue with short T_1, the vector returns to a position near the z axis between pulses, and then is carried slightly below the xy plane by the second pulse. In regions of long T_1, the vector returns only a short distance towards the z axis before the second pulse is applied and the second pulse carries the vector well beyond the xy plane. Because the strength of the MR imaging signal from a region depends on the component of the magnetization vector in the xy plane, the signal varies from one region to the next, following the second pulse, in a way that reflects the local T_1 value. The same process occurs following subsequent 90-degree pulses.

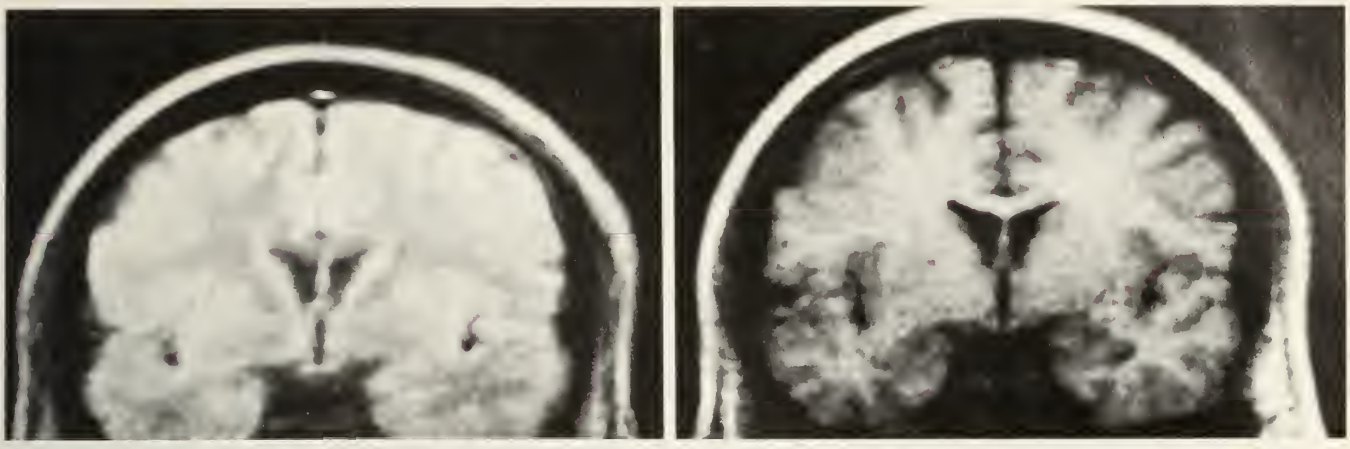

Figure 5.—Saturation recovery images: **Left,** A saturation recovery scan with a repetition time of 2 seconds reflects primarily proton spin density. **Right,** The same slice imaged with a repetition time of ½ second is T_1 weighted and yields more contrast (courtesy of Technicare Inc).

By increasing the TR to a value greater than the average T_1 of the sample, saturation recovery images can be weighted by proton density to reveal the hydrogen content of the sample. With a long TR, the magnetization vector returns completely to the z axis between pulses and is rotated exactly into the xy plane with each radiofrequency pulse to yield a maximum signal uncontaminated by relaxation effects (Figure 6). With a shorter TR, the image is weighted by both proton density and relaxation times (principally T_1), leading usually to an enhancement of image contrast. Saturation recovery and other imaging methods can be made to reflect blood flow because blood flowing perpendicularly to the image section will partially or completely leave the section between radiofrequency pulses. The motion of blood can increase or decrease image intensity, depending on the choice of pulse sequence and interpulse times. Increased intensity is observed within the lumen of blood vessels as the TR interval is decreased in saturation recovery scans. Saturation recovery scans with a short TR are also useful in highlighting regions with long T_1s, including cysts and subdural fluid collections.

Inversion recovery imaging is a two-pulse sequence with many clinical applications. The first pulse is a 180-degree "inverting pulse" that rotates the magnetization vector from the +z axis onto the −z axis (Figure 7). Relaxation then occurs for an inversion time before the second pulse, and the magnetization vector relaxes toward the +z axis at a rate determined by the local T_1 value. The second pulse is a 90-degree "read" pulse; the signal is measured immediately following this second pulse.

A magnetization vector that has relaxed quickly toward the +z axis because of a short T_1 is carried beyond the +z axis by the read pulse. Its projection onto the x (or y) axis is positive and so is the signal it generates, leading to a white appearance. A region of tissue with a long T_1 has a magnetization vector that relaxes only slightly before the read pulse. This vector falls short of the +z axis when the read pulse is applied, and its projection onto the x (or y) axis is negative, yielding a negative signal and a dark image.

Compared with saturation recovery images, inversion recovery images are weighted more heavily towards T_1. They are useful particularly when high image contrast is desired, such as in distinguishing white and gray matter in the brain. A variety of white matter diseases and edema, all of which have prolonged T_1s, appear as dark regions in inversion recovery images. Inversion recovery imaging may prove especially useful for the early detection of disease processes that involve white matter. Its discrimination of white matter tracts is also helpful in locating lesions that cause displacements of the tracts.

Spin-echo pulse sequences were developed specifically to show the spin-spin relaxation time, T_2. In T_2 measurements, a problem arises because magnetic inhomogeneities of any

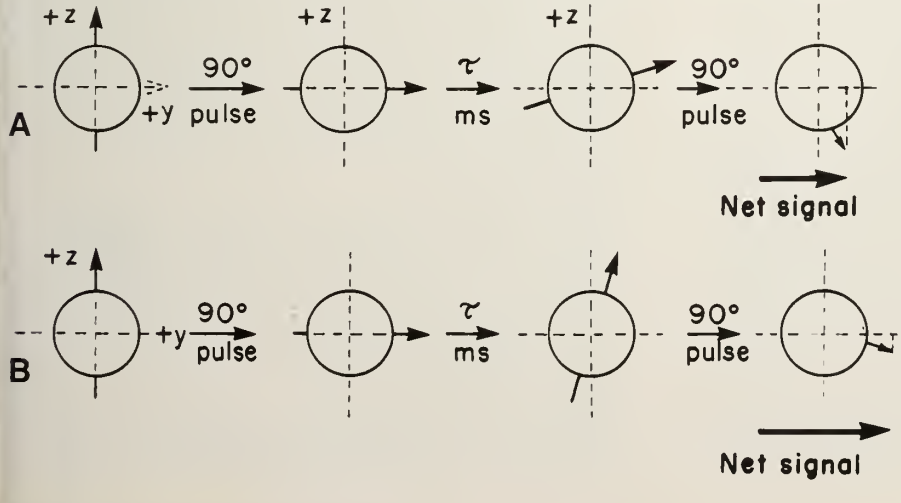

Figure 6.—**A,** Regions with a long T_1 yield a small signal after the second pulse because the magnetization vector relaxes just slightly in the +z direction between pulses. **B,** Regions with a short T_1 relax nearly to +z between pulses; these regions yield a strong saturation recovery signal. τ = interpulse time.

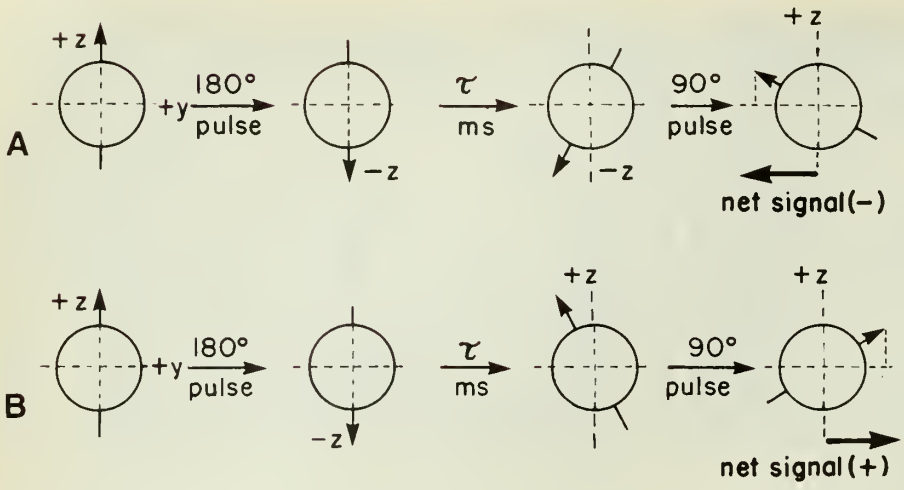

Figure 7.—Inversion recovery: **A,** Regions with a long T_1 yield a magnetization vector that relaxes only slightly toward the +z axis in the interpulse delay inversion time. These regions yield a negative signal. **B,** Regions with a short T_1 relax more and yield a positive signal. τ = interpulse time.

kind produce spin dephasing. The inhomogeneities of interest arise from spin-spin interactions of nuclei; however, these inhomogeneities are weak compared with those from other sources. No magnet produces a completely homogeneous field, especially over a volume as large as the human body; even in the best magnets, variations in the magnetic field are much stronger than those caused by spin-spin interactions. In addition, the applied magnetic field is made even more inhomogeneous by application of the additional magnetic fields needed for spatial information. In measurements of T_2, machine-induced inhomogeneities cause an artificial dephasing of the magnetization vector and must be neutralized.

The spin-echo sequence begins with a 90-degree pulse to rotate the magnetization vector into the xy plane (Figure 8). Magnetic field inhomogeneities then cause the vector to dephase into components in various orientations in the xy plane. After an interpulse delay time, which is so short that little T_1 relaxation occurs, a second pulse is applied to rotate the components through 180 degrees. After inversion, components of the magnetization vector that had been diverging in the direction of faster spin (counterclockwise) are positioned to converge upon the other components. These components still represent regions where the magnetic field is more intense and, hence, are still precessing faster. Similarly, regions that are precessing more slowly are positioned ahead of the other components of the magnetization vector after inversion. These components continue to precess more slowly. After inversion, the continued counterclockwise motion of all of the components now closes the dephasing fan instead of widening it, and the components converge to reconstitute the original signal or, more properly, its 180-degree "echo." This reconstitution occurs over a time 2TI = TE—where TE is the echo delay time and TI is the interpulse time—because the components of the vector take just as long to converge as they did to diverge. In the spin-echo technique, the machine-generated magnetic inhomogeneities act as long in one direction as in the other, and they cancel. Spin-spin interactions, however, produce fluctuating inhomogeneities that cannot be cancelled with any degree of precision.

In the spin-echo technique, successive echoes are generated by applying additional 180-degree pulses. The magnetization vectors that come together to form each new echo

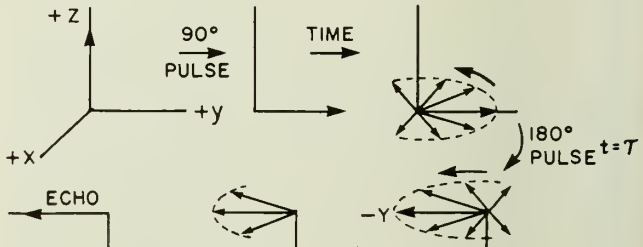

Figure 8.—Formation of a spin echo. The magnetization vector begins to dephase after the initial (90-degree) radiofrequency pulse. Following the inverting pulse, the vector components converge to form an echo free of machine effects at the echo time, which is double the interpulse time.

are given more time for spin-spin interaction; this time causes them to fan out in a way that is not neutralized by the spin-echo process. A "snapshot" of the magnetization vectors at the return of each echo shows a progressive dephasing due to true spin-spin relaxation, independent of machine-generated inhomogeneities. Because the reduction in signal intensity between echoes is due mainly to true spin-spin relaxation, measurement of the relative strengths of two successive echoes allows T_2 to be calculated.

With a pulse repetition time that is long compared with T_1, the influence of T_1 on the spin-echo imaging signal is reduced and the signal reflects principally the spin-spin relaxation time T_2, modulated somewhat by proton density. As the repetition time is shortened, the influence of T_1 on the signal intensity is increased. Spin-echo images appear to be very sensitive to a variety of abnormalities because many disease processes produce significant changes in T_2.

Making an Image

The encoding of an MR imaging signal with spatial information is one of the more complex aspects of MR imaging, and the task of understanding it is complicated further by the practice of different manufacturers to use different methods. The methods described here illustrate the principles involved; most manufacturers use some combination of these principles.

In an MR imaging unit, the imaging plane may be selected by applying an alternating magnetic field perpendicular to

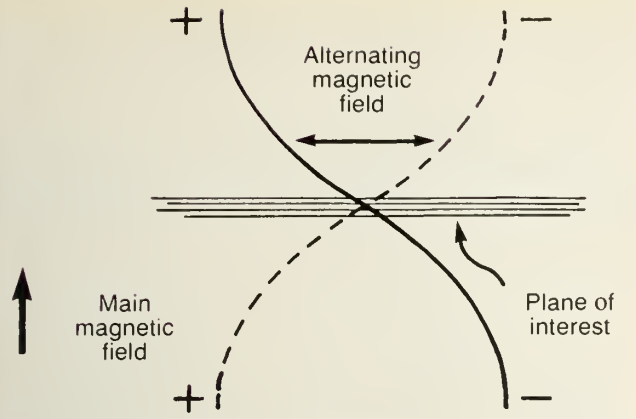

Figure 9.—How a section of tissue is selected for imaging: An alternating magnetic field causes the resonance frequency at most points to change with time. The magnetic field and resonance frequency are unaltered only at "nodal" points" that lie in the section of interest. The signal from this plane can be electronically extracted from the rest of the signals by filtering out components that vary with time.

the main magnetic field. The alternating field causes the total magnetic field at most points to vary with time (Figure 9). In response, the frequency of the imaging signal from these points varies with time, increasing as the field increases and decreasing as the field decreases. At "nodal" points in a narrow zone that defines the region of interest, the total magnetic field remains constant and the signal frequency does not vary with time. By filtering out signal components that vary with time, the signal from the region of interest can be extracted. By electronically moving the nodal point while changing the direction of the applied field, contiguous transaxial, sagittal or coronal (or other) images can be obtained without ever moving the patient.

Another method of plane selection is to apply a smaller, additional magnetic field (called a gradient) across the sample. The gradient is designed so that it reinforces the main field at one side, subtracts from it at the other side, varies smoothly in between and does not change with time. The gradient alters the field only along one axis, and the magnetic field remains constant in each plane perpendicular to the direction of the gradient. The magnetic field, and therefore the resonance frequency, is different in adjacent planes perpendicular to the gradient. Hence, a radiofrequency pulse with a narrow, "selective" range of frequencies affects only the tissue in a single planar section. This process is called "selective irradiation" (Figure 10).

Once a section is selected, further manipulations of magnetic gradients separate the signals from different points in the section. A gradient can be applied across the section of interest so that it adds to the field on one side and subtracts from it on the other. The main magnetic field is unaltered only along a line perpendicular to the direction of the gradient. In Figure 11, this line is labeled the central line. Lines parallel to the central line in the image section will yield an MR imaging signal of higher or lower frequency compared with that of the central line. When signals are received, they are separated into different frequencies wherein each frequency represents the signal from a particular line in the section. At each frequency, the signal intensity represents the contribution of all points in a line parallel to the central line. The representation of a signal from a line as a single

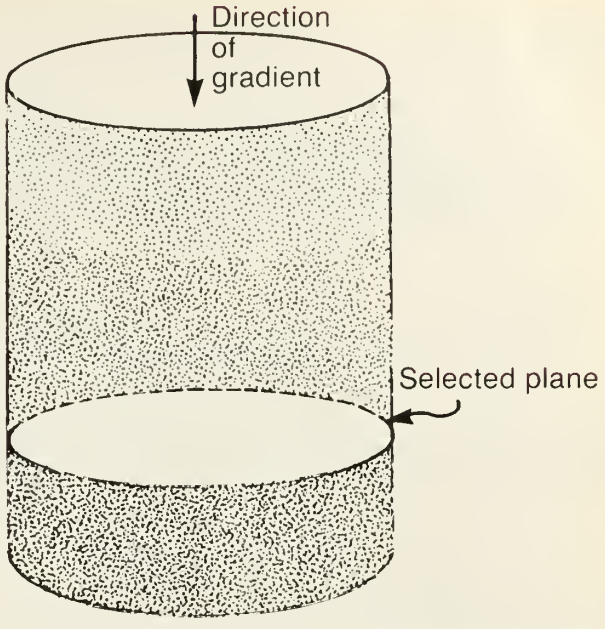

Figure 10.—A magnetic gradient is added to the main magnetic field, causing it to vary smoothly from one end of the sample to the other. In any plane perpendicular to the gradient, all points experience the same magnetic field and have the same resonance frequency. Adjacent planes experience different magnetic fields and have different resonance frequencies. Radiofrequency pulses with a narrow range of frequencies induce resonance only in the plane with the appropriate resonance frequency.

value in a distribution of frequencies is a type of projection. By electronically rotating the magnetic field gradient around the patient in the section of interest, these data can be reconstructed into an image. The reconstruction technique is analogous to the image reconstruction process used in CT. In MR imaging, it is called zeugmatography; this approach was the first reconstruction process used in this imaging technique.

The most common method of magnetic resonance imaging is termed two-dimensional Fourier transformation (2DFT).[9] A fixed gradient is applied to the selected image plane, and a second perpendicular gradient is applied briefly (Figures 11 and 12). The effect of the second gradient is to momentarily speed up or slow down the precession in each line defined by the fixed gradient. Along a given line, each magnetization vector rotates faster or slower, depending on its position. This process introduces phase differences among vectors at different points in the line; hence, each point is localized in terms of an x coordinate described by phase and a y coordinate identified by the resonance frequency. Increasing the strength of the second gradient in many small steps during a scan eventually provides the computer with enough information to do a Fourier transformation and make an image. This particular imaging technique is free of the linear type of motion artifact common in CT images. Instead, the 2DFT technique introduces a generalized blurring in the image when motion is present, sometimes accompanied by minor vertical streaks.

The same principles can be extended to a three-dimensional Fourier transformation process that permits simultaneous collection of data from an entire volume of sample. Each volume element (voxel) in the data set is a 1- to 2-mm cube, whereas the voxel size of planar methods is 1 to 2 mm

square in the plane of interest and of selectable thickness in the depth dimension. The principal advantage of the volumetric method is that once the data have been collected, they can be dissected into 1- to 2-mm thick slices in any orientation, provided that computer storage is adequate. In planar methods, a separate scan is required for each orientation. The major disadvantage of the volumetric method is the rather long time required for data collection.

Imaging Times

Imaging times are significantly longer in MR imaging than in CT, primarily because the MR imaging signal is weak and easily obscured by electronic noise. To extract the MR imaging signal from noise, it is necessary to repeat the radiofrequency pulse sequences several times for each projection. The principal sources of noise are commercial radio stations,

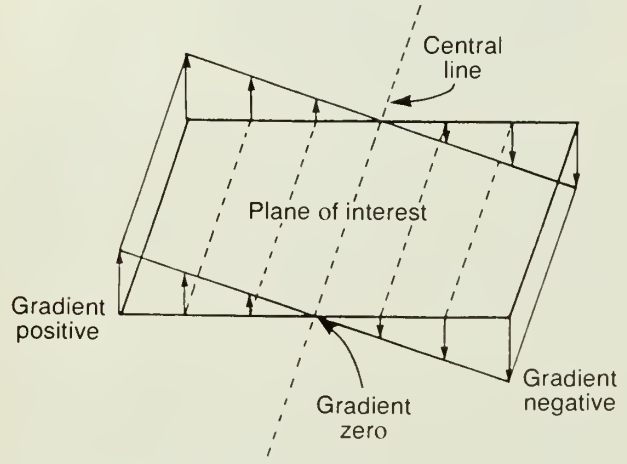

Figure 11.—The magnetic gradient applied across the plane of interest is positive (adds to the main magnetic field) on one side and negative (subtracts from the main field) on the other. The main magnetic field is unaltered along the central line. Each line has a frequency characteristic of a particular magnetic field intensity, and each point on the line contributes to the strength of the signal at that frequency. Rotating the gradient leads to a series of projections that can be reconstructed into an image.

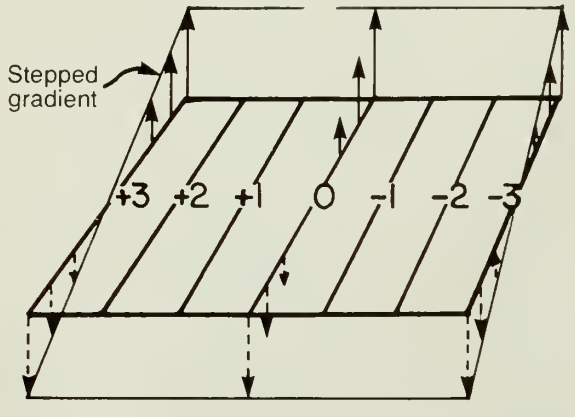

Figure 12.—Two-dimensional Fourier transformation: A plane is selected and a gradient applied as shown in Figure 11. Line "zero" is the central line. The other lines are numbered to indicate the strength of the gradient. A second gradient (shown) is applied perpendicular to the first and introduces a phase shift in the signal from each line. The second gradient is increased stepwise for subsequent pulse sequences while the first gradient remains fixed. Fourier transformation of the magnetic resonance imaging data then yields an image.

fluorescent lights, electric motors, electrical connections and microprocessors within the MR imaging equipment and thermal noise from within the patient. The external sources can be reduced by enclosing the imaging unit in a copper-clad room and by installing electronic filters to remove low-frequency—that is, 60-Hz—noise. Electrical connections can be replaced by optical coupling devices. Patient noise is not so easily controlled and presents a fundamental limit to reducing imaging time. Evidence suggests that increasing the intensity of the magnetic field increases the strength, as well as the frequency, of the MR imaging signal; hence, higher magnetic field intensities may permit the use of shorter imaging times. Current scanners operate with field strengths from 0.07 to 2 tesla (T) (0.7 to 20 kilogauss). Improvements in the design of radiofrequency transmitting and receiving antennas may help reduce scan times somewhat, but significant progress in shortening scan times probably will come slowly. A significant improvement in imaging time has resulted from the development of techniques to collect data simultaneously for many slices.

Many disease processes produce changes in more than one MR imaging variable (for example, many processes affect both T_1 and T_2). That is, MR imaging has several "windows" through which abnormalities can be detected. To detect a disease process and characterize it in terms of changes in T_1 and T_2, one or more scan techniques should be chosen that are considered optimal for the particular process. A complete MR imaging examination could take several minutes for data collection, with additional time needed to review one set of images and to select a subsequent scanning method. One major avenue of current research in MR imaging is the appearance of various disease processes in different images, so that eventually protocols can be established to tailor scan techniques to particular clinical situations.

The Magnets

Three types of magnets are used in MR imaging units: permanent magnets, operating at field strengths of up to 0.3 T; resistive magnets, operating up to about 0.15 T, and superconductive systems at above 0.35 T. Each of these magnet types generates a magnetic field that is many thousands of times stronger than the earth's magnetic field.

Resistive magnets use significant amounts of electrical power to maintain the magnetic field, and must be water cooled to remove the heat generated by the dissipated electricity. Resistive magnets cost about $100,000, operate with relatively few problems and produce magnetic fields that are somewhat less stable and homogeneous than those from superconducting systems (Table 2). These systems yield high-quality images but are expensive to operate because of their power consumption.

Superconducting magnets consist of a cylindrical coil of tin-niobium alloy wires embedded in a copper matrix and surrounded by a vacuum Dewar. They cost more than $200,000, produce exceptionally stable and homogeneous fields and yield somewhat better spatial resolution and soft tissue contrast. They also are somewhat less expensive to operate, even though they must be cooled to within a few degrees of absolute zero by liquid helium. They draw no electrical current once the magnetic field is established. Although manufacturers have considerable experience

TABLE 2.—*Characteristics of Magnets Used in Magnetic Resonance Imaging*

Magnet Type	*Field Strength*	*Costs*	*Advantages*	*Disadvantages*
Resistive	≤ 0.15 T	Initially $100K or less, but power costs are high.	Fewer site restrictions; possibly less down time	Lower field strengths; less spatial resolution
Superconductive	≥ 0.35 T	$200K or more	Better soft tissue contrast and resolution	Increased fringe fields; dependence on superconducting technology.
Permanent	≤ 0.3 T	$150K or more, depending on field strength; operational costs minimal	Almost no fringe fields; minimal power and coolant; dependable operation	Weight; extraction of magnetizable materials; uniformity of field (?)

building large superconducting magnets, the units still are not entirely immune from potential problems. For example, a vacuum leak could cause a slight rise in temperature of the windings and lead to a sudden loss of superconductivity. Heat generated by the circulating current as it suddenly encounters electrical resistance conceivably could damage the magnet. Superconductive magnets used in MR imaging are designed to prevent serious damage resulting from a loss of superconductivity.

Permanent magnet units operate without extensive requirements for either electrical power or liquid helium coolant. They are essentially free from mechanical failure. Their initial cost, however, is somewhat greater than the investment required for a resistive or superconductive system of comparable field strength. However, they are subject to resolution losses associated with nonuniformities in the magnetic field and problems associated with extraction of a metal object, should one become captured between the pole pieces. In one permanent magnet system, the developer has devised a clever method to tune the magnetic field to improve its uniformity. With one commercial unit using a permanent magnet, the weight of the system (100 tons) could be a disadvantage under certain circumstances.

Resistive and superconductive (but not permanent) magnets generate strong fringe fields that can turn nearby magnetizable objects, such as scalpels, screwdrivers and oxygen tanks, into flying objects. At distances of a meter or two, a magnet can erase the magnetic strip on a credit card; at 9 or 10 m it can distort the display of a video monitor and cause certain types of cardiac pacemakers to malfunction. Any structural steel within 4 or 5 m of the center of a large magnet can seriously distort its field uniformity and degrade the image. Elevators and other moving steel objects cannot be tolerated within several meters of an MR imaging unit. Because of steel beams in the floors and walls of most existing structures, some vendors recommend a separate building for MR units, especially those using higher field strength magnets. Other manufacturers insist that problems of structural steel near an MR imaging unit are more imaginary than real. Experience with several MR imaging installations in a variety of settings to date appears to support this viewpoint. Sometimes it is possible to correct for field distortion by adding shimming magnets at specific locations around a unit.

The weight of many MR imaging magnets can create high structural loads, restricting the MR imaging unit to the basement in many buildings. Even if a suitable site in a hospital is found, major construction may still be required because a superconducting magnet cannot be separated into smaller sections for installation (resistive and permanent magnets can). Therefore, it may be difficult to move a superconductive unit into the site.

Small steel objects can produce significant image artifacts if they are near the region of the body being scanned. Dental fillings usually are nonmagnetic and do not cause artifacts, though gold fillings sometimes introduce minor distortions. Orthopedic implants usually are made from a nonmagnetic chromium-cobalt alloy and do not degrade the image. Surgical clips are stainless steel and usually have no significant magnetic properties; some clips do introduce slight distortions, however, perhaps because variations in the manufacturing process can produce microscopic regions of magnetism within the clips. Some aneurysm clips undergo a torque when in the main field, and this may be hazardous enough to exclude some patients from MR imaging examination.[11]

MR Imaging Safety

Although there is no evidence to date that MR imaging causes any biological harm, there still are areas to investigate.[12] Possible bioeffects fall into three main categories: the effects of high-intensity static magnetic fields, the minute electrical potentials and currents induced by changing magnetic fields or by blood flow in a static field and possible heating from the radiofrequency pulse.

Four mechanisms of possible harm have been identified for the intense static magnetic fields used in MR imaging. First, strong fields can produce torque on biologic materials causing, for example, reorientation of sickled erythrocytes at fields of 0.35 T[13] and reversible changes in the shape of retinal rods at 1 T.[14] Changes in the conformation of enzymes produced by this mechanism conceivably could lead to alterations in enzyme kinetics or membrane permeability. Second, magnetic fields might affect the velocity of nerve conduction. Third, motion through a magnetic field will induce small electrical potentials and currents in a conductor, possibly affecting biological electropotentials. Fourth, T-wave changes have occurred in electrocardiograms during exposure to high magnetic fields.[15] The latter changes are proportional to the field strength and have not been shown to cause permanent physiologic changes. They are either the result of electrical potentials produced by blood flowing in the magnetic field, or possibly an artifact of the measuring technique.

Laboratory animals have been exposed to 1 T fields continuously for up to 28 days[16] without any noticeable effects. Intrauterine exposure of animals[17] also has produced no observable effect, and human leukocytes displayed no chromosomal changes at fields up to 1 T.[18] Workers in particle

physics laboratories have been exposed to fields of 5 T for an average of three days per year for several years without any sign of harm.[19] Taking these and other factors into account, the Food and Drug Administration (FDA) of the US Department of Health and Human Services has established guidelines for MR imaging safety that state that fields up to 2 T appear to be safe.[20]

Electrical currents can be induced in tissue by the varying magnetic fields used for spatial encoding of MR imaging data. The effects of these currents vary significantly, depending on the waveform of the field changes, their amplitude, time duration and repetition rate. Most studies suggest that the oscillation frequency and amplitude of magnetic fields used in MR imaging are low enough to preclude any harmful effects. Because of their low threshold, visual sensations called phosphenes usually precede other bioeffects induced by changing magnetic fields. Phosphenes have not been induced in routine MR imaging work to date. Other effects of changing magnetic fields that have been evaluated include alterations in the action potential of nerves,[21] seizures[22] and cardiac fibrillation.[23] None of these effects are expected to occur within the limits set by the FDA (3 T per second). Induced currents can also cause tissue heating, but this source of heating is less significant than that from radiofrequency pulses. Metal objects might be heated more than tissue by changing magnetic fields because their greater electrical conductivity leads to higher induced currents. The heating of surgical clips and metallic prostheses has been investigated. Clips are not heated significantly by present MR imaging equipment, and although it appears that larger prostheses will not be heated significantly,[24] more work needs to be done.

Irradiation of the body with radiofrequency pulses heats tissue in the same manner as diathermy. FDA guidelines have established a limit of 0.4 W per kg of whole body exposure, which is half the rate of heat produced in tissues from basal metabolism and only 3% of the heat produced during heavy exercise. This level of exposure will not significantly increase core temperature because it does not strain natural mechanisms of heat loss to the air by conduction and evaporation. It has been well documented that radiofrequency pulses can decrease the binding of calcium in the brain. This may be a nonthermal effect[25] that occurs well out of the range of MR imaging intensities. There is some controversy about the production of permeability changes in the blood-brain barrier, but effects are not likely to occur below the limits established by the FDA.[12]

At the present time, two conditions are considered contraindicated for examination by MR imaging. These are pregnancy and dependence on a cardiac pacemaker. The recommendation that pregnant patients not undergo MR imaging examination is not a reflection of known effects on fetuses. Instead, it is considered a prudent policy until more is known about possible fetal effects. There is evidence that some types of artifact pacemakers are affected by magnetic fields similar to those used in MR imaging.

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Medical Staff Conference

Fat Embolism Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *It has been our custom to invite each chief medical resident to present a topic at a Medical Staff Conference near the end of the academic year. In that tradition, Dr Martin L. Serota will now review for us the syndrome associated with fat embolism. Dr Serota received his medical degree from the University of California, San Francisco, and then completed three years of medical residency at the University of California, Los Angeles, before returning here as chief medical resident. We greatly appreciate the leadership that he has brought to our patient care and teaching programs during this past year. Dr Serota.*

Report of a Case

DR. SEROTA :† The patient, an 18-year-old man, was in a motor vehicle accident and sustained a fracture of his right femur and tibia. He suffered no head or thoracic trauma. He was afebrile with a normal blood pressure and pulse. On examination his right lower extremity was found to be shortened and externally rotated. Laboratory findings included a hematocrit of 41%, an arterial oxygen partial pressure (PaO_2) of 75 mm of mercury and a normal-appearing chest radiograph (Figure 1). Roentgenograms of his right lower extremity showed closed fractures of the femur and tibia.

He was admitted to the orthopedic service and 12 hours later was noted to have tachypnea, tachycardia and confusion. The temperature was 38.8°C (101.8°F); he was disoriented to time and place. The PaO_2 was now 57 mm of mercury. He was given supplemental oxygen and corticosteroids were administered intravenously. Twelve hours later conjunctival petechiae were noted.

A repeat chest radiograph showed diffuse bilateral pulmonary infiltrates (Figure 2). One day after admission he be-

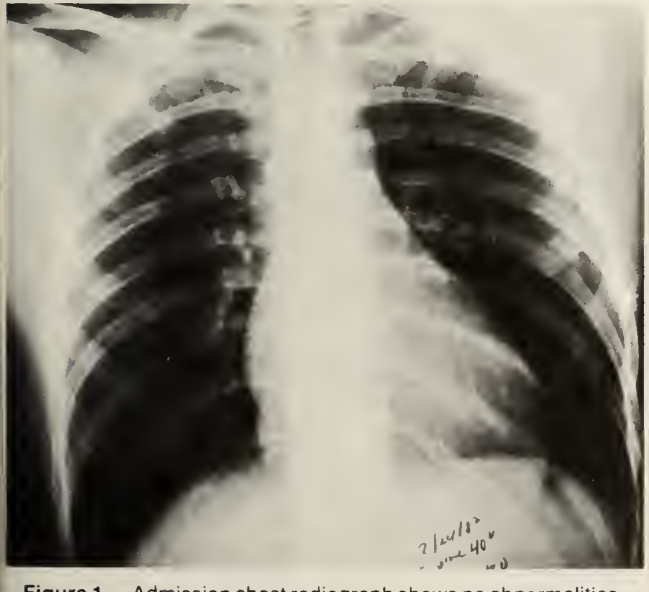

Figure 1.—Admission chest radiograph shows no abnormalities.

Figure 2.—Chest radiograph taken one day after admission shows diffuse bilateral pulmonary infiltrates.

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Serota ML: Fat embolism syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 1984 Oct; 141:501-505)

ABBREVIATIONS USED IN TEXT
CT = computed tomography
PaO_2 = arterial oxygen partial pressure

came more agitated and confused with an extensor toe sign on the left; the PaO_2 was 63 mm of mercury with the patient receiving 50% oxygen concentration by mask. An endotracheal tube was inserted and after a computed tomographic (CT) scan of the head showed no abnormalities, he was transferred to the respiratory care unit. Mechanical ventilation was started with a positive end-expiratory pressure of 5 cm of water. Decerebrate posturing and bilateral extensor toe signs were noted.

On the third hospital day his respiratory and mental states were improved. His hematocrit had dropped to 28% and the platelet count was 50,000 per μl, down from 167,000 per μl at the time of admission. The next day weaning from the respirator was begun. On the fifth hospital day new petechiae were noted in his axillary folds and the platelet count had returned to near normal. Positive end-expiratory pressure was discontinued and on hospital day 6 the endotracheal tube was removed. The patient was alert but depressed and withdrawn. The following day he was transferred back to the orthopedic service for open reduction and internal fixation of his fractures. He gradually returned to his baseline affect and respiratory state with normal chest radiographic findings before discharge.

History

The history of the fat embolism syndrome dates to 1862 when Zenker first discovered fat droplets in the pulmonary circulation of a railroad worker dying of a crush injury.[1] The first clinical diagnosis was made in 1873, when von Bergman treated a man with a fractured femur in whom respiratory distress developed and who went into coma and ultimately died. Postmortem examination showed fat droplets in the lungs.[1] The first report in America came from Fenger and Salisbury in 1879.[1] About 50 years later the two major theories of the origin of the fat droplets were proposed—Gauss's mechanical theory and the physiochemical theory of Lehman and Moore.[1] These are discussed below.

Pathophysiology

Two major puzzles in the fat embolism syndrome concern the origin of the fat found in the pulmonary vascular bed and the factors that mediate tissue injury in the lung and other organs.

The mechanical theory of fat generation proposes that trauma to the bone marrow disrupts fat cells and tears the fragile veins in and around the fracture site. These factors facilitate entry of neutral fat into the venous circulation where it travels to the pulmonary vascular bed via the inferior vena cava. The physiochemical theory postulates that the stress of trauma causes a release of catecholamines such as epinephrine, which mediate mobilization of free fatty acids from adipose tissue and induce coalescence of chylomicrons and other serum lipids. Fat microglobules are formed and, as in the mechanical theory, must reach the lung via the venous circulation.

Both theories have some support. Evidence in favor of the mechanical theory is severalfold: (1) The fat embolism syndrome is seen most commonly with trauma severe enough to cause fractures and rarely in other settings of stress[3]; (2) during hip replacements fat can be detected entering the venous circulation simultaneously with insertion of the femoral component of the prosthesis[4]; (3) the fat and cholesterol composition of a fat embolus is similar to that of the bone marrow adipose tissue but unlike that of the serum,[5,6] and (4) bone marrow cells and spicules can sometimes be found with fat in the lungs of trauma patients, especially those sustaining rib fractures.[7] There are some situations, however, that cannot be explained entirely by the mechanical theory of fat generation. For example, fat emboli may be found in the lungs at autopsy despite no history of trauma. This has been described in cases of pancreatitis, burns, sepsis[3] and other conditions (Table 1). Also, the degree of fat embolization in some cases exceeds the amount of fat present in the fractured bone, necessitating a contribution of fat from some other source. Thus, the mechanical theory best explains the origin of the fat in most cases of fat embolism syndrome, but in other settings physiochemical or metabolic pathways may play a role.

Once the fat reaches the lung by any mechanism it is not irreversibly trapped, as some have thought,[2] but rather it circulates between the pulmonary and systemic circulation.[22] The low-pressure pulmonary circulation acts as a bottleneck

TABLE 1.—*Fat Embolism*

	Source
Conditions commonly associated with fat embolism and occasionally with fat embolism syndrome	
Fracture of femur or tibia	
Total hip or knee replacement	Spengler et al, 1976[8]; Bisla et al, 1976[9]; Mallory and Kolodzik, 1976[10]
Lymphography	Andersen et al, 1977[11]
Conditions that have been associated with fat embolism but rarely, if ever, with fat embolism syndrome	
Other fractures	
Median sternotomy	Wukasch et al, 1975[12]
Cardiopulmonary resuscitation	Buchanan and Mason, 1982[7]
Blood transfusions	Shier and Wilson, 1980[13]
Bone marrow transplantation	Paradinas et al, 1983[14]
Intravenous fat emulsion infusion	Levene et al, 1980[15]
Cardiopulmonary bypass	Shier and Wilson, 1980[13]
Corticosteroids	Katz et al, 1983[16]; Pastore and Kessler, 1982[17]
Sickle cell anemia	Tsou and Katz, 1977[18]
Sickle cell-hemoglobin C disease	Tsou and Katz, 1977[18]
Fatty liver	Randall, 1980[19]
Pancreatitis	Johnson and Tong, 1977[20]
Diabetes mellitus	Shier and Wilson, 1980[13]
Sepsis	Shier and Wilson, 1980[13]
Burns	Shier and Wilson, 1980[13]
Renal transplantation	Shier and Wilson, 1980[13]
Acute decompression sickness	Kitano and Hayashi, 1981[21]

for the fat, temporarily slowing it during its course through the vascular system so that at any one point in time, most is localized in the pulmonary vessels. As more pulmonary capillaries are occluded by fat, pulmonary pressures rise, opening arteriovenous shunts that allow passage of fat globules to the left-sided circulation. The fat then passes through the visceral organs where some may be deposited, with the remainder returning to the pulmonary circulation through the venous system.

How fat mediates tissue injury is not understood, though several possible explanations exist. It has been postulated that neutral fat is deposited in the lungs where pulmonary lipase degrades it into free fatty acids that promote lung injury.[23] In experimental animals, free fatty acids appear to have a direct and immediate toxic effect when injected intravenously. Early pulmonary findings include edema, capillary congestion and polymorphonuclear leukocyte infiltration of the alveolar septa. Gross hemorrhage and septal necrosis are usually seen within 12 hours and hyaline membrane formation and fibrosis are late findings.[24] In addition, neutral fat microglobules might accumulate fibrin and platelets causing microthrombi to form in the lung. These microthrombi would mediate the release of vasoactive amines and prostaglandins resulting in local vasoconstriction. Tissue thromboplastin released from the injured bone marrow might also contribute to a hypercoagulable state in the lung. However, neither neutral lipid nor free fatty acid injected alone into experimental animals adequately reproduces the manifestations of fat embolism syndrome, indicating additional contributors to its pathogenesis.

Recent work in the adult respiratory distress syndrome suggests that the polymorphonuclear leukocyte may be a mediator of lung injury in conditions such as fat embolism. Experimental models of adult respiratory distress syndrome show leukostasis in the lung,[25] augmented neutrophil adherence to endothelial membranes, release of oxygen radicals and proteases by the neutrophil and elaboration of products of the lipoxygenase pathway such as leukotrienes resulting in lung injury.[26] This injury can be prevented by mechlorethamine hydrochloride-induced neutropenia.[26] Complement activation has been suggested as one possible mechanism of neutrophil activation.[27] How the cascade of events is initiated in cases of adult respiratory distress syndrome or fat embolism syndrome is not yet known; fat may not be the responsible agent, but rather serves as a marker of significant injury.

Clinical and Laboratory Findings

Fat embolism, unlike fat embolism *syndrome*, is a common event. It probably occurs in more than 90% of cases of fracture[23] and joint replacement procedure.[4] It may result from exogenous sources of fat such as lymphography,[28] blood transfusions, bone marrow transplantation[14] or intravenous fat emulsion infusion.[15] Fat embolism also takes place in many other medical conditions such as fatty liver, pancreatitis, sepsis and burns (Table 1). Even cardiopulmonary resuscitation causes fat embolism and may explain why some patients without known trauma have fat in their lungs at autopsy.[7] However, the fat embolism *syndrome* rarely occurs in other than trauma cases.

The fat embolism syndrome characteristically begins 12 to 72 hours after injury, but may occur within a few hours or after several days. Patients usually present with one or more of the following symptoms and signs: dyspnea, low-grade fever, tachypnea, tachycardia and altered mental state. In half the cases a specific evanescent petechial rash can be seen in nondependent portions of the body such as the chest, anterior axillary folds and conjunctiva. Without close and frequent observation the rash may pass unnoticed. Retinal examination may show a variety of abnormalities including exudates, cotton-wool spots, perivascular hemorrhages and intravascular fat.[29]

Laboratory findings include hypoxemia, thrombocytopenia, anemia and hypocalcemia. Although the PaO_2 may be normal on admission, it invariably falls with development of the clinical syndrome. The hypoxemia may be mild and transient, or can be quite profound, requiring high concentrations of supplemental oxygen as well as intubation. The hematocrit, platelet count and serum calcium level often fall for unknown reasons with development of the syndrome but rarely cause problems in management. Thrombocytopenia may be due to a low-grade consumptive coagulopathy, platelet aggregation or adherence of platelets to fat microglobules. The fall in hematocrit may result from intrapulmonary sequestration of erythrocytes in addition to trauma-related blood loss. One could also postulate that free fatty acids and neutral fat bind serum calcium en route to the lungs causing transient hypocalcemia, but progressive hypocalcemia remains unexplained. We still do not have satisfactory explanations for the laboratory abnormalities.

The chest radiograph shows abnormal findings in about two thirds of patients with fat embolism syndrome. The most common finding is a diffuse bilateral interstitial or alveolar infiltrate, sometimes described as a "snowstorm" pattern. The infiltrate may be patchy and is often more peripheral than hilar; there should be no evidence of pulmonary vascular redistribution or pleural effusion unless other disease processes are present.[30]

Many laboratory tests elicit findings considered characteristic of fat embolism syndrome. These include fat globules in the sputum, urine or blood, and a raised serum lipase level.[1,23] These findings are entirely nonspecific, however, and are found in trauma patients with and without the syndrome.[15]

In a patient with trauma resulting in multiple fractures but without shock or other injuries in whom hypoxemia, confusion, petechial rash and diffuse pulmonary infiltrates develop one to two days after the injury, a clinical diagnosis of fat embolism syndrome can usually be made. Other disorders must be considered in the differential diagnosis, however. The pulmonary infiltrates may be due to hypervolemia, pulmonary contusion, neurogenic or cardiogenic pulmonary edema, aspiration pneumonia and sepsis or other causes of adult respiratory distress syndrome such as shock. One must also be cautious not to overlook a correctable structural central nervous system lesion in a trauma patient with an altered mental state.

Course and Prognosis

The manifestations of fat embolism syndrome can be quite various. They can range from a transient asymptomatic pete-

chial rash to mild dyspnea lasting a few hours, to profound hypoxemia, respiratory insufficiency and death. The syndrome appears to be more severe with multiple rather than single fractures and with associated hypovolemia. The prognosis appears to totally depend on the respiratory state of a patient, as recovery from fat embolism syndrome follows the improvement in respiratory function.

As mentioned above, fat embolism syndrome is a systemic disease with possible fat emboli in every organ of the body, especially the lung, central nervous system, kidneys and skin. However, organ dysfunction has only been reported for the lung and the central nervous system. Manifestations of the latter can be dramatic, ranging from confusion to coma, and may include seizures, hemiparesis, hemiplegia and decerebrate posturing. Fortunately, if a patient survives the respiratory insult, the neurologic dysfunction is almost always reversible.

The survival rate of fat embolism syndrome has improved dramatically over the years and this appears unrelated to the advent of any one specific therapy. The mortality of fat embolism syndrome in the 1950s and early 1960s in several large series was consistently 15% to 20%.[1,31,32] This has improved steadily since, with mortality from fat embolism syndrome now quite rare.[33-35] This impressive advance in survival appears to coincide with the institution of specialized intensive care units in major hospitals and parallels the improved survival seen in poliomyelitis victims and other patients requiring specialized respiratory care.[36,37] The prognosis may be worse in the elderly and in patients who have underlying cardiopulmonary disease.

Therapy

The cornerstone of therapy in fat embolism syndrome is supportive care. Early attention should be paid to trauma patients to correct volume losses while avoiding overhydration and to immobilize fractures. The PaO_2 should be monitored closely and supplemental oxygen should be given as needed. Patients with severe respiratory problems may need intubation and mechanical ventilation. Positive end-expiratory pressure appears to be useful in treating the hypoxemia. Unproved and potentially harmful therapies of the past have included intravenous administration of 5% ethanol and heparin and giving low-molecular-weight dextran and high-dose corticosteroids. Use of the former three has largely been discontinued.

Corticosteroids deserve special mention because they are still used in the treatment of fat embolism syndrome. Ashbaugh and Petty[38] in 1966 first described their experience with two patients who appeared to benefit from very modest doses of hydrocortisone given intravenously. Subsequently, corticosteroids have become widely accepted for treatment of fat embolism syndrome despite the lack of any controlled study of their efficacy. In fact, there is evidence that patients fare just as well with supportive care alone,[33,35] in addition to rare case reports of patients in whom corticosteroids may have contributed to the development of fat emboli.[16,17]

Two recent studies have shown a beneficial effect of corticosteroids in preventing fat embolism syndrome if given shortly after trauma.[39,40] Both studies were prospective and randomized and large doses (30 mg per kg a day for one to three days) of methylprednisolone were used. Development of fat embolism syndrome occurred almost exclusively in the group of patients not receiving methylprednisolone and no adverse effects were attributed to the corticosteroids. However, it is premature to advocate the widespread use of corticosteroids to prevent fat embolism syndrome in trauma patients because the overall incidence of clinically important fat embolism syndrome is quite low, mortality with modern supportive care is virtually nil and the adverse effects of high-dose corticosteroids in patients with trauma are not yet known.

Conclusion

Fat embolism is a common occurrence, but the clinical syndrome of fat embolism is relatively rare. The fat embolism syndrome is a distinct and systemic process that may occur in cases of trauma or nontrauma. In either instance it can be difficult to differentiate from other pulmonary disorders. The search for a sensitive and specific diagnostic test has been unrewarding and the diagnosis continues to be based on clinical findings. The disorder can be managed by good supportive care only, with very low mortality. High-dose corticosteroids appear effective prophylactically if given within a few hours after trauma, but their widespread use cannot be advocated until it has been shown that the benefits from their use outweigh the risk of infection and other possible complications.

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Epitomes

Important Advances in Clinical Medicine

Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in allergy that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Platelet-Activating Factor

THE MOST RECENTLY recognized and possibly the most potent cell-derived mediator of inflammation and bronchoconstriction is platelet-activating factor (PAF). This name was derived in the early 1970s when it was learned that leukocytes from allergic rabbits exposed to a specific allergen produced a substance capable of aggregating and inducing secretory activity of platelets. Rabbit and human plasma and serum contain an enzyme (PAF acetylhydrolase) that rapidly destroys platelet-activating factor. Acidification of plasma to inactivate this enzyme has permitted the detection of PAF during anaphylaxis in rabbits and in association with urticaria in humans. The structure of PAF was discovered almost simultaneously by three independent laboratories in 1979. It is a novel ether phospholipid mediator with the structure 1-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine known as AGEPC or PAF-acether.

PAF is not preformed or stored in cellular granules, as is the case with histamine. Instead, it is newly synthesized following the appropriate stimulation of a variety of cells. Human cells known to produce PAF are neutrophils, eosinophils, monocytes, macrophages, alveolar macrophages, endothelial cells, platelets themselves and possibly basophils and mast cells. Although named PAF because of its effects on platelets, this mediator elicits many other important inflammatory and physiologic events: polymorphonuclear leukocyte aggregation, chemotaxis and enzyme secretion, stimulation of monocytes, hypotension, contraction of bronchial and visceral smooth muscle and increased vascular permeability. Many of these activities are independent of platelet activities. Injecting PAF into human skin induces immediate skin blanching indicative of acute vasoconstriction, which is often associated with burning pain and pruritus. An intense histamine-like wheal and flare reaction then develops, reaching a maximum intensity after 10 minutes and subsiding within 60 minutes after administration. PAF-induced vasoactive effects occurred at concentrations at least 1,000 times less than was required for histamine. PAF is 600 times more potent than leukotriene D_4 (or slow-reacting substance of anaphylaxis) and 20,000 times more potent than histamine in causing airway reactivity in rhesus monkeys.

The exact role of PAF in human disease remains to be proved and clarified. However, very recently it has been learned that PAF is released into the venous blood of patients with acquired cold urticaria when their arms are immersed in ice water. This is the first demonstration that PAF is released during a human disease event but there is still no proof of a causal relationship between the release of PAF and the urticaria.

In summary, PAF has proved to be an extremely potent mediator of a variety of physiologic and inflammatory events in animals, subhuman primates and humans. It is the subject of a great deal of current investigation that includes its possible role in human disease and a search for molecules that will either block the effects of PAF on target cells or prevent its release after a variety of stimuli.

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Pinckard RN: Platelet-activating factor. Hosp Pract 1983 Nov; 18:67-76

Long-Acting Theophyllines

LONG-ACTING theophylline preparations, designed for once-a-day dosing in relatively healthy adults who have asthma, have become available for prescription usage in the United States within the past year. These sustained-release medications provide stable therapeutic blood concentrations, effective bronchodilation and bioavailability similar to the twice-a-day theophylline preparations with, for some patients, the added convenience of once-a-day administration. Long-acting theophyllines can usually be given in one daily dose equal in milligrams to the daily dose of a shorter-acting theophylline preparation. Although the primary toxicities of the long-acting theophyllines are those from theophylline in general, so that precautions in methylxanthine administration apply to all types of theophylline preparations, additional precautions pertain to long-acting, once-a-day theophylline preparations.

Smokers metabolize theophylline very quickly and often require twice-a-day administration of the "24-hour" preparations. The elderly, those with congestive heart failure and those who have hepatic dysfunction are at an increased risk for toxic effects due to slow theophylline metabolism and therapy should be started at low doses and their blood concentrations monitored carefully. Manufacturers recommend that a single dose of sustained-release theophylline be given in the morning due to variations in drug levels with posture, activity and food intake. Because very large doses of some theophyllines taken with meals may result in erratic gastrointestinal absorption and unpredictable theophylline blood concentrations, taking the daily dose on awakening—one to two hours before breakfast—may eliminate this potential problem. Twice-a-day preparations may provide more stable blood theophylline concentrations in some patients requiring large theophylline doses.

When acute bronchospasm necessitates urgent theophylline therapy, an immediate-acting theophylline preparation or intravenous administration of aminophylline (theophylline with ethylenediamine) is indicated. Long-acting theophylline preparations should be reserved for long-term theophylline maintenance therapy particularly when improved patient compliance and convenience are of concern. They are well tolerated and may be used safely by monitoring serum theophylline concentrations and clinical responses.

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Neutrophil Chemoattractant Receptors and Inflammation

THE IMPORTANCE of neutrophils (polymorphonuclear leukocytes) in the inflammatory process has been appreciated for more than a century, and yet the mechanisms by which they are able to carry out directional locomotion into sites of tissue inflammation is poorly understood. In the past seven to eight years a great deal of knowledge has been accumulated that indicates that the locomotory or chemotactic ability—as it is most often referred to—of neutrophils is due to the presence of specific cell surface receptors for chemoattractants, that is, chemicals towards which the cells move in a directed manner. There is good evidence that many of the functions that the neutrophils carry out as part of their inflammatory activities—such as migrating into the tissues, engulfing foreign bodies, increasing oxygen metabolism and production of toxic oxygen species and microbial killing—are initiated through receptor-mediated cell activation.

A number of chemoattractant receptor systems have been described on the surface of neutrophils, each of which appears to be separate and non-crossreacting and yet all lead to common pathways of cell activation and must therefore be linked at some postreceptor point.

Receptors for fragments of the fifth component of complement ($C5_{fr}$) are considered extremely important in directing neutrophils into areas of inflammation where complement activation is felt to be an important aspect of the disease pathophysiology, such as serum sickness, immune vasculitis and cryoglobulinemia. There is also very good evidence that complement receptor-induced neutrophil activation and subsequent pulmonary leukostasis are important in acute lung injuries (shock lung syndrome) associated with trauma or sepsis.

The most extensively studied chemoattractant system is that for synthetic *N*-formylated peptides that are felt to be identical or closely related to naturally occurring bacterial products and thus are important as a model of neutrophilic response to infection. Studies of the formyl peptide receptor system have shown that certain anti-inflammatory agents (especially glucocorticoids) may affect neutrophil function through interactions at the receptor level in addition to their numerous other biologic actions.

Another chemoattractant receptor has been described for a chemotactic factor produced by neutrophils themselves after ingestion of sodium urate or calcium pyrophosphate crystals. Neutrophil activation by this receptor has been postulated to be an important amplification system contributing to the acute inflammation often seen with crystal-induced arthritis.

Most recently, there has been great interest in the role in inflammatory reactions of lipid molecules generated from arachidonic acid, especially the hydroperoxy and hydroxy fatty acids (HPETEs and HETEs) and leukotrienes produced through the action of a lipoxygenase enzyme. In neutrophils, hydroperoxyeicosatetraneoic acids (HPETEs) are further metabolized to a group of compounds termed leukotrienes. The leukotrienes possess potent inflammatory activities and include the sulfidal peptide constituents of slow-reacting substances (C_4, D_4 and E_4) and the dihydroxy leukotriene B_4. Goldman and Goetzl have recently shown a distinct and specific receptor for leukotriene B_4 on neutrophils, and they and others have elucidated the functional responses of neutro-

phils to leukotriene B_4. Although much is still unknown regarding the role of the leukotrienes in inflammation, their potency and ubiquity make them strong candidates as inflammatory mediators or modulators in many disease processes involving recruitment of inflammatory cells. Present efforts are being directed toward the development of specific inhibitors of leukotriene formation. Such agents would be very useful for basic research on the interaction of arachidonic acid metabolites and of great therapeutic potential in the treatment of asthma, rheumatoid arthritis or other related conditions.

Elucidation of increasing numbers of surface receptors for diverse chemoattractants on neutrophils, together with the understanding that the various neutrophil functions are triggered by occupation of these receptors, provides basic information for a clearer understanding of neutrophil function in inflammatory conditions and will likely provide clinicians with more disease-specific and effective therapies in the near future.

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Clinical Significance of Helper/Suppressor T Cells

THE MORPHOLOGICAL determination (typing) of the percent and absolute number of circulating T-"helper" and -"suppressor" lymphocytes has gained widespread popularity with the development of monoclonal antibodies to detect antigens on the surface of different subpopulations of human lymphocytes. In this context, the terms T "helper" and "suppressor," which are functional terms, are gross oversimplifications. The helper T cells, as detected by the monoclonal antibodies in general use such as T4, contain not only helper cells for immunoglobulin synthesis but also inducer cells for many T-cell functions and even the precursors of some suppressor T cells. Thus, the T-helper/inducer population is really a mixture of related but distinct T cells. These distinctions based on function can be delineated immunologically by other monoclonal antibodies not in general use. Similarly, the suppressor T cells defined by monoclonal antibodies such as T8 comprise a variety of cell types involved in cytotoxicity and in inhibition of immune responses.

The measurement of helper and suppressor T-cell numbers, percents and ratios can be compared with the measurement of different types of leukocytes by differential cell count. Values may be abnormal in many cases but the clinical utility is limited to a very small number of disorders. Furthermore, while the test is very sensitive, it is also nonspecific, being altered in many infectious (especially viral), metabolic, neoplastic, rheumatologic and congenital and acquired immunologic disorders. Quantitation of helper/suppressor T cells may be clinically useful in certain suspected immunologic disorders. In infants, it can be used to distinguish between transient hypogammaglobulinemia (reduced helper T cells) and congenital agammaglobulinemia (normal helper/suppressor T cells and absent B cells). In adults, T-cell subsets are most often measured in the evaluation of persons suspected of having the acquired immune deficiency syndrome (AIDS). While a reduced number (and percent) of helper T cells with a normal or increased percent of suppressor cells is almost uniformly found in patients who have AIDS, these findings are very nonspecific and, in themselves, not diagnostic. Moreover, altered helper/suppressor T-cell ratios are found after a viral infection and in many sexually active homosexual men who do not have AIDS. Thus, while an abnormal helper/suppressor T-cell ratio is a characteristic immunologic finding useful in confirming the diagnosis of AIDS, it is by no means diagnostic of the disorder. In other adult immunodeficiencies, such as common variable immunodeficiency, T-cell subsets (by the generally used markers) are often abnormal but appear to have no relationship to the in vivo or in vitro functional defects observed.

Measurement of helper/suppressor T cells is not a screening test. In selected patients with possibly abnormal T-cell function, it should be used in conjunction with other tests of immune function such as a battery of delayed hypersensitivity skin tests. It is important to emphasize that patients should not be labelled as having an "immune disorder" or "dysfunction" solely on the basis of an in vitro morphologic determination of helper/suppressor T cells.

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Penicillin-Induced Anaphylaxis

OF AN ESTIMATED 400 to 800 anaphylactic deaths per year in the United States, as many as 75% have been ascribed to penicillin sensitivity. Anaphylaxis may occur in one to four instances per 10,000 patient treatment courses. The death rate is about 1 to 2 per 100,000 patients treated. The oral route appears to be the safest but reactions and even death have occurred from penicillin taken orally. Children are at lower risk than adults.

Penicillin is the only drug whose allergenic metabolites have been identified. The penicilloyl moiety, formed in largest quantity and thus called the major determinant, is responsible most often for accelerated urticarial reactions. A skin test reagent for detecting sensitivity to this determinant is available commercially as penicilloyl-poly-

lysine. Some ten other antigens comprise the minor determinants but test reagents for these are not available for routine use. IgE antibodies to penicilloate and other minor determinants are associated with anaphylactic sensitivity. Preformed conjugates and self-polymers that may be present in penicillin preparations are thought by some investigators to play a role in penicillin anaphylaxis.

The presence of penicillin-specific IgE is conveniently and rapidly shown by immediate wheal and erythema skin testing. Although sometimes a screening procedure, penicillin skin tests are usually done in patients who require penicillin for a serious infection and who have a history of penicillin allergy. Prick followed by intradermal tests is done with penicilloyl-polylysine, various concentrations of the aqueous fresh penicillin to be used and proper controls. Significant reactions to subsequently administered penicillin are unlikely in skin test-negative patients. Persons without a history of penicillin allergy have a 7% or less incidence of positive skin tests. Clinical histories suggestive of IgE-mediated reactions yield a 17% to 46% positive skin test rate, depending on the type of previous reaction and the time elapsed between the reaction and skin testing.

Past sensitivity wanes with time and future sensitization may occur anytime. Consequently, skin testing is relevant only to a current clinical situation. It is safe when properly done. In vitro testing for specific IgE to penicilloyl by radioallergosorbent test is promising because it would avoid the rare instance of reaction to skin testing, but it does not predict anaphylaxis.

In cases in which penicillin is still considered the drug of choice in the face of a positive skin test, desensitization may be done. Oral as well as parenteral methods have been proposed. Parenterally given desensitization is effective but cumbersome and can be associated with severe life-threatening reactions. Oral desensitization appears to be effective and relatively safe. It is usually accomplished with less severe reactions.

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Diseases of Cilia

THE SIGNIFICANCE of ciliated epithelium in both health and disease of the human respiratory tract has been increasingly appreciated. Mucociliary clearance, a process highly dependent on the coordinated metachronal movement of cilia, is an important mechanism for protecting the upper and lower airways. Both primary and secondary types of ciliary dysfunction have now been described.

A primary defect in the ultrastructure of cilia, normally represented as nine pairs of peripheral microtubules around two central ones, appears to be important in the pathogenesis of the immotile cilia syndrome, a hereditary disease clinically characterized by bronchiectasis, sinusitis and situs inversus in half the cases (termed Kartagener's syndrome when the latter is present). Cilia in this disorder have congenital abnormalities in the microtubular apparatus necessary for normal ciliary beating. The most common specific defect seen on electron microscopy is absence of the dynein arms—structures that facilitate intermicrotubular attachment and reattachment, resulting in bending of the cilium. Other ultrastructural variations include absence of the radial spokes and transposition of the microtubules. The diagnosis is usually made in adults with a history of chronic pulmonary or sinus disease (or both); some men present with infertility due to immotile sperm. Ultrastructural defects of cilia are also found in children who have not only the expected sinopulmonary problems, but also chronic otitis or a history of neonatal respiratory distress syndrome. One case of a different type of a primary ciliary abnormality, the isolated absence of nasal cilia, has been described. The affected boy had problems with persistent rhinitis and either chronic sinusitis or undeveloped sinuses.

Secondary or acquired disorders of cilia can occur due to various external influences inducing changes in ciliated respiratory epithelium. Ciliary dropout and damaged cilia along with decreased mucociliary clearance have been seen in patients who have allergic rhinitis after local nasal antigen challenge. Similarly, tracheal mucous transport rates, as measured by a technique using labelled Teflon particles, are diminished in patients with asthma, and antigen challenge causes further impairment. This dysfunction may be due to a ciliary inhibitory factor in sputum, possibly a leukotriene, though mucous changes are more likely to be the determining factor in asthma. Long-term cigarette smoking can lead to ciliary changes including swollen, compound cilia and even cilia with "9 plus 2" ultrastructural aberrations. Short-term cigarette smoke exposure can either diminish or enhance mucociliary clearance, the latter probably due to direct parasympathetic stimulation by nicotine. Chronic sulfur dioxide exposure, topical nasal decongestant use, aspirin administration and *Mycoplasma* infection have all been associated in humans or animals with either cilia detachment or decreased mucociliary activity, or both, thereby possibly compromising nasal and lung defense mechanisms.

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Topically Applied Corticosteroids and Cromolyn Sodium in Managing Rhinitis

CORTICOSTEROIDS are effective in treating various forms of rhinitis. The usefulness, however, of this class of drugs has been severely hampered by the profound side effects occurring as a function of time, dosage and individual sensitivity. In an effort to circumvent this problem, efforts have been directed toward the development of topically applied glucocorticoids capable of effecting a high degree of potency while being absorbed in insufficient amounts to cause adrenal suppression or cellular toxicity.

Three topical corticosteroids have been approved in the United States for the treatment of rhinitis and a fourth is currently undergoing clinical trials. Dexamethasone phosphate (Decadron Turbinaire) induces some adrenal suppression at a dose of 1 mg per day (12 inhalations), thereby limiting its usefulness. Beclomethasone dipropionate (Vancenase or Beconase) has the advantage of slow absorption from mucous membranes and rapid metabolism, lending a significant degree of freedom from adrenal suppression at its therapeutic dosage range of 400 to 600 μg per day (8 to 12 inhalations). Flunisolide (Nasalide), like beclomethasone, is free of significant adrenal suppression at therapeutic dosages (200 to 300 μg or 8 to 12 inhalations per day) due to its "first pass" mechanism of elimination and a short half-life of 1.8 hours. Recent clinical trials with fluocortin butyl have shown similar efficacy and safety data.

Cromolyn sodium is a mast cell stabilizer that has proved relatively efficacious and very safe in the treatment of allergic bronchial asthma. It has recently been marketed as an intranasally given solution (Nasalcrom) for the treatment of allergic rhinitis. Clinical trials have indicated that it is probably as effective as antihistamine. Its usefulness is limited by frequent applications (four to six times per day). Furthermore, both cromolyn sodium and the topical corticosteroids do not usually produce an immediate response. This is important to emphasize when prescribing the medication because patients will expect a "nasal spray" to produce immediate dramatic improvement; similarly, usage "as needed" should be discouraged in favor of a regular regimen.

The choice of medication should be predicated in part on the severity of the disease, the presence or absence of polyps and the patient's prior response to medication. For example, Nasalcrom might be an effective medication in a patient who had excellent response to antihistamines but could not tolerate the drowsiness. On the other hand, if antihistamines are clearly ineffective or nasal polyps exist then a topical steroid such as beclomethasone or flunisolide should be considered.

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Rhinometry

NORMAL INSPIRATORY CURRENTS first enter the nasal alae, then turn upward through the nasal valve and pass across the inferior and middle turbinates into the nasal pharynx. Fully 60% of an inspired breath, about 300 ml (presuming a tidal volume of 500 ml), is inhaled 16 to 20 times per minute; cold, dry air is warmed to about 30°C (86°F), moistened to 80% humidity and filtered. Under normal conditions and quiet breathing, there is an alternating cyclic activity within the two nares. A normal healthy person inhales the vast majority of inspired air through one nostril, due to the erectile tissue causing shrinking of the nasal turbinates on one side while the opposite turbinates are filling and thus partially occluding the other nostril. Deflections of the septum, masses in the nose or hypertrophy of the mucous membrane will obstruct the air flow. When partial bilateral obstruction occurs, the patient may perceive this as fluctuating unilateral obstruction.

Rhinometry is the measurement of nasal air flow. Air flow rate (V) is determined by the patency of the passage, the manner in which the air flows (laminar or turbulent) and the pressure difference (ΔP) from the external atmospheric pressure to the retronasal space.

Many methods have been used to measure nasal patency. Any acceptable technique requires the continuous measurement of V and ΔP. One currently popular technique is anterior rhinometry, so called because all measurements are obtained from the external surface of the nose. A pneumotachometer calibrated for flow rate is fitted with a plastic rubber-tipped nosepiece. This is placed against the opening of one nostril. As the patient inspires, air moves through the pneumotachometer. A pressure tap on the pneumotachometer measures external nares pressure. Another similar nosepiece is placed against the opposite nostril. This one is connected to a pressure transducer that records the pressure within the nostril, reflective of the retronasal pressure. The signal from it is viewed on an oscilloscope, an XY recorder or a direct digital readout instrument. When a satisfactory recording has been obtained, the tubes are switched to measure the other nostril. Anterior rhinometry has the advantages of being simple to do (even small children may be easily measured), rapid (takes less than 30 seconds) and informative about the patency of each nostril. Furthermore, the values are readily reproducible when done by an experienced technician.

A second method is posterior rhinometry. It requires the retronasal pressure to be measured from a tube in the mouth. This technique usually uses a face mask fitted with a pneumotachometer. Generally, posterior rhinometry is more expensive and complicated. While some patients can do the maneuver immediately, others have to be trained to relax their tongue to allow the oral cavity to communicate with the retronasal space. Also, the mask technique provides only a total reading of air flow for the two nasal passages.

Another technique to measure nasal patency uses the Wright peak flow meter. This system evaluates nasal function during expiration, which seems less logical than

inspiratory studies because patients complain of inspiratory difficulties when congested. In addition, the important nasal functions of air conditioning, cleaning and olfaction are carried out during inspiration. It should be noted that inspiratory flow values differ from expiratory because of the negative airway pressure and the flaring of turbinates into the airstream during inspiration. The least desirable aspect of this technique is that forceful expiration blows secretions into the measuring instrument.

Rhinometry can be valuable in medical practice. Clinically, the technique is useful in documenting and monitoring the degree of nasal obstruction. In diagnostic work it can help differentiate impairment due to structural or mucosal changes by obtaining values before and after a nasal decongestant; similarly, challenge studies can confirm the etiologic role of various inhalants. It may also be helpful in determining the effectiveness of medication or surgical treatment.

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The Radioallergosorbent Test

THE DIAGNOSIS and management of atopic allergic disease depends on correlating historical and physical findings with identification of IgE antibodies specifically directed at one or more allergens. Knowledge of specific antigen sensitivity is important in directing environmental controls, in predicting exacerbations (after exposure to pertinent antigens) and in planning appropriate immunotherapy when indicated. The radioallergosorbent test, or RAST, is the most commonly used in vitro assay for detecting these antibodies.

RAST is a sandwich-type radioimmunoassay. Allergen-specific IgE in a serum sample binds solid-phase coupled allergen usually on a paper disk. An anti-IgE antiserum will "sandwich" the bound IgE. After washing, the amount of radioactivity is proportional to the amount of specific IgE in the serum sample. Results are expressed semiquantitatively and are assigned to classes based on comparison with reference sera.

For clinical use, skin testing is generally considered more sensitive than RAST. Attempts to increase RAST sensitivity by lowering thresholds or by modifying the scoring system have generally led to an unacceptable number of false-positive results. RAST is, however, preferable to skin testing in selected instances. Patients with a history of anaphylaxis, especially some with pronounced food sensitivities, are at risk for exacerbation with skin testing, whereas those with severe dermatoses may present insufficient normal skin to permit accurate testing. Dermatographic patients may wheal and flare on a non-IgE mediated basis making skin testing uninterpretable. It is generally agreed that skin testing is contraindicated during pregnancy and that RAST is an acceptable alternative. Infants and toddlers with atopic disease are physiologically capable of immediate hypersensitivity responses on skin testing and can be tested reliably. However, some children are made so anxious by procedures, even the minimally painful prick-puncture test, that RAST may be better tolerated. RAST carries no patient risk and may be performed in patients on antihistamines.

The radioallergosorbent test methodology has been useful in identifying the immune consequences of immunotherapy and for isolating and identifying allergenic components. Fractionated antigens can be assayed in RAST inhibition assays, in which soluble antigen competes with solid-phase antigen for antigen-reactive IgE. This method has also been successful in precisely quantitating potency of allergenic extracts, the more allergenic in the extract the greater the inhibition of the RAST. Such identification and quantification are crucial for the development of standardized allergen extracts. Establishing dose requirements for immunotherapy by RAST is currently under study, but present practice generally uses skin testing with pertinent antigens before instituting this therapeutic modality.

Skin testing has historically been less expensive, more flexible and more available than RAST. A number of commercially available technological variations of RAST now exist. However, the American Academy of Allergy and Immunology has warned of the potential for abuse in the form of questionable marketing tactics and poor quality control, which could lead to unnecessary testing and increased medical costs.

Despite the availability of new in vitro systems, skin testing is still less expensive and more sensitive and remains the standard for allergen-specific IgE detection; RAST must be regarded as a supplemental technique. Either method requires that a physician be trained in the use and the interpretation of these tests. The detection of allergen-specific IgE is only meaningful when it correlates with a patient's illness.

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Venom Immunotherapy in Children

THE DEVELOPMENT of purified Hymenoptera venoms for the diagnosis and treatment of venom hypersensitivity has been a major advance in the care of allergic patients. To date, most information regarding this potentially lethal disorder (50 to 200 persons die each year in the United

States) has been gathered in adults. Skin tests or a radioallergosorbent test, supplemented by a questionnaire, in adults has shown that 4% of the population has a history of sting reaction, and 20% has evidence of venom-related IgE antibody. Patients with positive skin tests and no history of prior reaction have about a 5% reaction rate to subsequent sting, and those with a history and a positive skin test about a 60% reaction rate. Thus, in adults there is a high incidence of sensitization and a predictable maintenance of responsiveness justifying venom immunotherapy for systemic reactivity.

Similar studies have yet to be fully carried out in children. One prospective analysis of children with mild systemic reactions (urticaria) has found, however, that venom reactivity in children is less fixed than in adults. Thus, instead of a 60% re-reaction rate, a systemic response developed to a second sting in only 10% of children who had a known prior Hymenoptera reaction. Moreover, none of the subsequent reactions were more severe than the initial one. In venom-treated children, the re-reaction rate is less than 10% and the severity of reactions is greatly diminished. Of particular diagnostic difficulty are reactions that ensue after stings in the face and neck, which cause larger local reactions and rapid absorption of venom with the potential for severe but possibly non-IgE-mediated reactions.

At present it is prudent to institute venom immunotherapy for skin test-positive children who have severe systemic reactions to Hymenoptera venom and in those few children whose mild systemic reactions are increasing in severity. The duration of such therapy is currently under study but present practice is to prescribe long-term, potentially lifelong, treatment. For those children manifesting a single mild reaction or repeated but stable or diminishing mild reactions, a watch-and-wait attitude (supplemented by providing an anaphylaxis treatment kit and education in its proper use) has been supported.

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Eosinophils

THE EOSINOPHIL is a bone marrow-derived polymorphonuclear leukocyte found in blood (normal level, less than 300 per μl) and tissues in increased numbers primarily in allergic and parasitic disorders. The eosinophilia associated with immune events is T-lymphocyte-dependent and due to bone marrow stimulation by a specific eosinopoietic factor. Localization of the eosinophil to particular target organs is mediated by a variety of factors that selectively chemoattract the eosinophil. These factors include mast cell granule constituents, lymphokines, complement fragments, products of arachidonic acid metabolism (leukotriene B_4, hydroxyeicosatetraenoate [HETE]) and platelet-activating factor (PAF). The unique functions of the eosinophil are a consequence of its special constituents. These include major basic protein (MBP), a 10,000-dalton peptide that comprises 25% of the total granule protein, another cationic peptide (ECP) of 20,000 daltons, a special peroxidase, a neurotoxin and a 17,000-dalton lysophospholipase that can crystallize to form Charcot-Leyden crystals. This latter enzyme and MBP are also found in human basophils.

Eosinophil functions are both homeostatic and inflammatory. In helminth infestations, eosinophils can kill parasite larvae by MBP/ECP and peroxidase-mediated reactions, hasten expulsion of adult worms from the gut and enhance secondary immunity. In allergic reactions, eosinophils are capable of degrading histamine, leukotrienes and ether lipids such as platelet-activating factor, binding heparin and ingesting mast cell granules. Exuberant eosinophil reactions release MBP and induce eosinophil production of PAF and leukotriene C_4. The latter two are potent vasoactive-spasmogenic mediators, whereas MBP can degranulate mast cells and also kill ciliated cells and thereby produce histologic features in the bronchus similar to those seen in cases of asthma.

The ability of glucocorticoids to reduce eosinophil levels may thus underlie some of their clinical efficacy in diseases such as asthma. The development of agent(s) selectively active on eosinophils or on the unique eosinophil functions and constituents should provide another avenue of therapy for diseases such as asthma in which this cell is prominent.

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Immunologic Aspects of Cystic Fibrosis

CYSTIC FIBROSIS is a common heritable disease often manifested by cough and wheeze and complicated by a high prevalence of nasal polyps (6% to 24%), which occur at an early age. For these reasons, cystic fibrosis is occasionally confused with respiratory allergy, particularly early in life. A sweat chloride test is always indicated in children with nasal polyps and should be considered in the initial evaluation of very young children who have respiratory signs and symptoms.

Chronic cough, wheezing and hyperirritable airways are common features of both cystic fibrosis and asthma. The two diseases may coexist. Indeed, there is an increased prevalence of atopy in patients who have cystic fibrosis, and the possibility exists that cystic fibrosis predisposes to clinical allergic disease. Certainly the clinical manifestations of allergic respiratory disease are of a more troublesome nature in the presence of cystic fibrosis. Physicians who care for patients with either disease must be constantly alert to the possible presence of the other.

In cases of cystic fibrosis, recurrent and chronic respiratory infections are major problems, particularly

those due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In advanced disease, more than 80% of patients harbor *Pseudomonas*. It is of interest that atopic patients with cystic fibrosis are more likely to have persistent colonization with *Pseudomonas* than are nonatopic patients with cystic fibrosis.

Colonization by *Aspergillus* species is also common in cases of cystic fibrosis. In the presence of asthma and cystic fibrosis, it is difficult to make a diagnosis of allergic bronchopulmonary aspergillosis because of overlap in clinical and laboratory features. Studies suggest a 5% to 20% incidence of allergic bronchopulmonary aspergillosis in patients who have cystic fibrosis. Positive sputum cultures, eosinophilia, precipitins to *Aspergillus fumigatus*, immediate or dual skin test reactivity, elevated total serum IgE levels and IgG antibodies to *Aspergillus* antigens are useful screening tests for allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Aspergillosis should be considered whenever significant pulmonary manifestations of cystic fibrosis do not respond to antimicrobial therapy. Clinical improvement and improved pulmonary function following corticosteroid administration may suggest the diagnosis of allergic bronchopulmonary aspergillosis.

Some but not all investigators have reported depressed leukocyte locomotion in cases of cystic fibrosis. Circulating immune complexes were also found to be increased in this disease, particularly during acute infections. The relevance of these findings to the pathogenesis and course of cystic fibrosis remains to be defined.

It is important for all physicians to recognize the immunologic aspects of cystic fibrosis, the similarity of its early manifestations to atopy, the frequent coexistence of atopy and cystic fibrosis and the possible enhancing effect of atopy to fungal growth. Increased understanding of immunologic mechanisms in cystic fibrosis may lead to improved patient management in the future.

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β-Adrenergic Agonists 1984

IN THE PAST DECADE several new drugs have been developed and marketed for the treatment of bronchial asthma that have improved β_2-specificity (bronchodilation greater than cardiac stimulation), that can be given by several routes of administration (oral, inhalation and parenteral) and that have a more prolonged duration of action (four to six hours) than epinephrine and isoproterenol. These improvements have come about by altering the basic catecholamine molecule. Changing the catechol nucleus to a resorcinol, such as metaproterenol sulfate or terbutaline sulfate, or salicyl alcohol (albuterol) decreases the agonists' susceptibility to enzymatic degradation resulting in more prolonged action and effective oral absorption. Increasing the size of the amino side chain substituent increases β_2-selectivity. β_2-Agonists are thought to have several actions in addition to bronchodilation, which make them useful in asthma, including inhibition of lung mast cell degranulation, increased mucociliary clearance and decreasing fatigability of diaphragmatic muscle.

Several recent studies have compared β-adrenergic drugs with theophylline for both acute and recurrent asthma. β-Agonists are superior to theophylline in alleviating acute asthma, whereas they compare favorably in controlling asthmatic symptoms over a several-week trial. In addition, when given simultaneously the effect of these drugs may be additive. Corticosteroids appear to restore β-agonist responsiveness in those who have become refractory, possibly by an increase in the rate of β-receptor synthesis.

In the oral form the newer β_2 drugs are more potent, selective and longer acting than ephedrine, which currently has little place in asthma therapy. Terbutaline (5 mg), fenoterol (5 mg) and albuterol (4 mg) are all comparable bronchodilators and more potent and selective than metaproterenol (20 mg). Although the efficacy of these agents has been shown in children 6 to 14 years of age, only metaproterenol is currently approved by the Food and Drug Administration for this age group. Epinephrine remains the most commonly used injectable sympathomimetic whereas terbutaline is also effective subcutaneously. Although theoretically advantageous, particularly in those with cardiac disease, terbutaline has not proved superior in children with acute asthma. Isoproterenol given intravenously is a useful treatment in children with respiratory failure and has not yet been replaced by the newer β_2-agonists.

The aerosol route of administration provides the greatest selectivity and effectiveness for β_2-agonists. Thus aerosolized metaproterenol from a metered-dose inhaler produces greater bronchodilation than the orally given form, though the dosage is only 10% to 20% of the oral dose. The onset of action and peak response are more rapid than with the oral form and side effects are less common, possibly because less drug is needed. The acrosol is also superior to the orally given form for exercise-induced asthma. Aerosols can be delivered by metered-dose inhaler or compressed-air jet nebulizer. Recently, auxiliary delivery systems using the metered-dose inhaler with spacers or reservoirs have been developed and show promise particularly in younger patients. Metaproterenol, terbutaline and albuterol are available in the metered-dose inhaler form, while metaproterenol solution is available for the jet nebulizer and can be used at home.

The most common side effects for the β_2-agonists are tremor and tachycardia. Because tolerance to these phenomena may occur after several weeks, one can begin with a reduced dose and gradually increase to the recommended dosage. Tolerance to the bronchodilator

response does occur, but the degree is not usually clinically significant unless these agents are used excessively. Such abuse is more likely to occur with the metered-dose inhaler with occasional serious consequences.

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Editorials

Physicians as Communicators

Elsewhere in this issue Ralph Crawshaw comments on his experience with what he terms clinical thinking or a clinical approach and the use of complex languages by government bureaucrats, health care providers and consumers as these relate to health planning. He notes that physicians do not always employ their clinical thinking or communication skills in their encounters with planners or consumers, and that planners often speak in "bureaucratese," physicians in "medicalese" and consumers in a language of personal experience with health care delivery, which he calls "pain and suffering." He points out that the last may be the most difficult to articulate but can be the most dramatically powerful in its effect.

There is much food for thought in all of this. An earlier editorial in these columns suggested a protocol for solving complex problems in health care by using an approach similar to that a physician uses in trying to solve puzzling or difficult problems in patient care. But that piece did not emphasize the all-important role of interpersonal communications in that problem-solving process. Too often, even in day-to-day patient care, physicians speak medicalese while their patients try to communicate with them in terms of pain and suffering. And, all too often, little or no real communication takes place. Where the approach is not one of genuine clinical collaboration between physician and patient, or if communication between them is less than adequate, there may be a substantial likelihood of an untoward outcome, such as poor patient compliance with the treatment program or a greater opportunity for the misunderstandings that can lead to malpractice actions.

Physicians can do little about bureaucratese, whether governmental or corporate, except to study it when necessary and hope to understand it. But physicians can do a lot to improve their own communication language, whether with patients, bureaucrats or the public. Medicalese is our own special lingo and is very useful for easy and often shorthand communication among physicians and other health professionals. But the truth is that it is not likely to be well understood by many patients or much of the public. We must learn to speak another language when communicating both with patients and the public. This language, if it is to be understood by them, will need to spell out in simple terms much of what medicalese takes for granted, and it will take more time for a physician to communicate using it. Some doctors are already very good at this patient- or public-oriented language, but there are too many others who are not. And there is little doubt that all of us could improve.

The ability of physicians to communicate and to approach patients and the public with a genuine intent to collaborate in problem solving is of the greatest importance. As physicians and the medical profession interact ever more closely with a still often rather hostile environment, it becomes essential.

MSMW

Mild Hypertension—Where Shall Treatment Begin?

Epidemiologically, the relationship between blood pressure and risk of coronary artery disease and stroke has no clear threshold. Risk rises progressively over nearly the full range of blood pressure levels found in the population. Clinically, however, the decision to treat requires the concept of a threshold above which the benefits of treatment outweigh any adverse drug effects and inconvenience. The problem is to choose the optimal level for this threshold in various age, sex and risk factors groups.

In this issue, Aagaard proposes that the threshold for drug treatment should be a diastolic blood pressure (DBP) of 105 mm of mercury. This is far higher than the levels chosen by other experts in the field, generally 90 in this country and 95 mm of mercury in Europe.[1] It is important to decide which of these policies is best because mild hypertension is a highly prevalent condition; in this country 25% of middle-aged men and women have a DBP greater than 90, while only 5% have levels above 105 mm of mercury.[2]

What kinds of evidence can best serve this judgment? Risk begins to rise substantially at 85 mm of mercury in prospective natural history studies. These studies, however, do not prove that the association is causal, or that risk is reversible, or that treatment will produce more benefit than harm. The main evidence for estimating the costs and benefits of long-term treatment comes from the large and lengthy randomized trials reviewed by Aagaard. We agree with him that these trials leave no question that treatment of patients with sustained diastolic blood pressures above 105 mm of mercury reduces risk of stroke as well as of malignant hypertension, renal failure, and hypertensive cardiomyopathy, without producing adverse effects of comparable magnitude.[3,4]

Clinical trials treating DBP between 90 and 105 are more problematic. Two have shown prevention of the electrocardiographic abnormalities found with left ventricular hypertrophy (LVH).[5,6] The Hypertension Detection and Follow-up Program (HDFP) has suggested that the rates of stroke and total mortality are reduced by treatment in every 5 mm stratum above 90 mm of mercury.[7] This study was not blind, and Aagaard's concern is that unintended cointerventions (blood pressure lowering drugs in the control group and extra nonspecific care for the intervention group) add some uncertainty to the conclusion that the 4 mm of mercury mean blood pressure differences between the groups was the cause of the 20% reduction in mortality. Fortunately, however, the Australian study, in which a single blind design controlled

for cointerventions, showed a 30% reduction in mortality and major morbidity for men with initial DBP of 95 to 105 mm of mercury.[8] We are more concerned by the Multiple Risk Factor Intervention Trial (MRFIT) study of intensive intervention on cholesterol and smoking as well as blood pressure which showed a tendency for the subgroup with DBP 90 to 94 mm of mercury at baseline to have higher mortality in the intervention than the usual care group. This, however, may have been due to an adverse effect of diuretic treatment in men with LVH type electrocardiographic abnormalities.[9]

An inherent difficulty in all these mild hypertension studies, which is not addressed by Aagaard, is the low disease event rate. Even with large sample sizes and long follow-up periods the trials have had insufficient power to produce statistically significant results in mild hypertension subgroups. The failure of the Veterans Administration and United States Public Health Service (USPHS) studies to reveal an effect on mortality is more likely due to low power than, as Aagaard contends, to lack of efficiency.

Aagaard points out that the placebo groups in blinded trials have provided useful information about the rates of spontaneous improvement and worsening of mild hypertension. Approximately 2% to 3% per year of patients with initial DBP between 95 and 110 develop sustained DBP greater than 110 mm of mercury.[5,10,11] On the other hand, in the Australian trial four patients receiving placebo became normotensive for every one whose hypertension became moderately severe. By the third year of follow-up 48% had DBP less than 95 mm of mercury.[10] This would suggest that it is prudent to delay initiation of drug therapy when DBP is less than 105 mm of mercury (to avoid treating the group with only temporary hypertension) were it not for the fact that some patients with persistent mild diastolic hypertension, if untreated, go on to develop early end-organ damage. Comparing drug treatment to placebo in the ten-year USPHS study, left ventricular hypertrophy developed in 13% versus 7% and retinopathy in 4.6% versus 0.5%.[5] If these findings were unrelated to prognosis or entirely reversible this would not be of concern. Unfortunately, the results of treatment are less good once patients have developed end-organ damage of this sort.[6,9]

It is rational to be concerned about the potential adverse effects of long-term treatment with antihypertensive medications. Diuretics and beta-blockers both adversely affect lipid risk factors.[12] Electrolyte abnormalities associated with diuretic usage may increase the risk of arrhythmias and interact with electrocardiographic abnormalities to increase the risk of sudden death.[9,13] No large scale trial has more than a decade of follow-up and this makes lifelong recommendations of these drugs an uncomfortable extrapolation, especially in younger patients.

Aagaard is also right in noting the possibility of serious problems with overly vigorous treatment of hypertension. In addition to the potential problem of inadequate coronary artery perfusion with low DBP, patients receiving higher diuretic doses have more pronounced electrolyte abnormalities, while those receiving higher beta-blocker doses have greater myocardial depression. On the other hand, Aagaard possibly overinterprets the findings of Stewart's observational study[14] of a greater incidence of myocardial infarction in patients with more pronounced blood pressure reduction with antihypertensive treatment. In an observational study it is impossible to distinguish drug overtreatment from drug unmasking of high risk persons with lower DBP due to poorer myocardial function.

Fortunately research in mild diastolic and systolic hypertension is continuing. The Medical Research Council (MRC) in Great Britain is in the midst of the largest double-blind placebo-controlled trial for mild hypertension to date, a three-armed trial that compares beta-blocker, diuretic and placebo as initial therapy. In this country elderly participants with isolated systolic hypertension are being recruited for a multicenter collaborative stroke prevention clinical trial.

In the meantime we tend to agree with many recommendations in the most recently released report from the Joint National Committee for the Detection and Treatment of Hypertension.[15] Mild hypertension that is confirmed at several clinic visits should be treated with dietary salt restriction and, if the patient is obese, weight reduction. Most patients whose DBP remains at levels of 95 mm of mercury or greater after an adequate trial of this approach will probably benefit from stepped-care treatment, beginning with a low dose of either diuretic or beta-blocker. Maximum diuretic dosages should be lower than those previously recommended.

Beyond this, it seems clear that drug treatment is particularly likely to be beneficial in those whose absolute risk is high, either because of age greater than 50 years or presence of other risk factors. In the light of the substantial rates of remission in mild hypertension, we also suggest that patients receiving long-term treatment periodically have their need for pharmacologic treatment reevaluated. A carefully supervised and tapered withdrawal of drugs several times each decade seems reasonably safe, and likely to benefit many patients by eliminating unnecessary and potentially toxic drugs.

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Benign Prostatic Hyperplasia in Humans

ELSEWHERE IN THIS ISSUE is an article on benign prostatic hyperplasia (BPH) by Cygan and Rucker in the Topics in Primary Care series. BPH is the most common benign proliferative abnormality found in any internal organ. It can be detected histologically by the third decade of life and by the ninth decade 88% of all prostates are affected. In all, 75% of men older than 50 years have symptoms of BPH and about one in four will require a prostatectomy.[1]

Despite the importance of BPH in the American population where life expectancy is significantly increasing, surprisingly little is known about the factors that cause nodular proliferation. Walsh believes that only two major factors are definitely known to be necessary for the onset of BPH—the presence of the testes and aging.[2] He has shown, for example, that one of the few hard endocrine facts previously thought to explain BPH in humans—a fivefold increase in dihydrotestosterone in BPH nodules compared with normal peripheral prostate—is an artifact caused by comparing surgical BPH nodules with normal prostate taken at autopsy. When both zones of the prostate are studied in fresh surgical specimens, the concentration of dihydrotestosterone is the same, about 5 ng per gram of tissue. Moreover, although the testes appear necessary for the development of BPH, it is important to recognize that the injection of testosterone stimulates prostatic epithelium but does not cause nodular hyperplasia (BPH). Thus, these two central observations in humans that (1) the dihydrotestosterone level is not increased in BPH tissue and (2) testosterone injections do not cause BPH, despite the fact that dihydrotestosterone is the major intracellular androgenic metabolite in the prostate, clearly suggest that regulatory factors other than androgens are involved in human BPH.

The measurement of steroid hormonal levels in the plasma of aging men suggests a 35% decrease in plasma testosterone concentration between 21 and 85 years of age without a concomitant change in plasma estrogens (estrone or estradiol).[3] Whether this change in the androgen-to-estrogen ratio with aging is related to BPH is unknown since men who do not have BPH cannot be readily identified in population studies.

It is likely that the induction and growth of nodular hyperplasia (note that the term "hypertrophy" is inappropriate) is dependent upon the interaction of multiple factors. Those factors responsible for the development of nodules may be different from those that later cause nodule growth to a clinically significant volume. McNeal has presented a cogent argument, based on extensive anatomic and pathologic observations, that BPH nodules originate from a specific anatomic region of the prostate that comprises not more than 5% of the gland and that this region shows morphologic features of abnormal embryonic development.[4,5] He believes that BPH nodule genesis results entirely from local tissue factors that are based on reactivation of an embryonic stimulus that resides in the stromal cells of the prostatic interstitial tissue. He indicates that nodule origin is random, both spatially and temporally. The central feature of nodule development is the focal formation of new glandular architecture, which he notes is exclusively an embryonic capacity. Synchronous growth of these nodules does not occur until 30 years later (in the seventh to eighth decade for most men). He would accept that hormones may accelerate nodule growth in this later period, and that certainly this is the time to seek specific changes in hormonal status, if they are present at all. McNeal's work serves as a reminder of the still basic role that careful histologic and pathologic observations have to play in a medical world currently dominated by molecular biology and sometimes, if not often, spinning its wheels. To be sure, I have limited these editorial comments on BPH to what is known—or I suppose to what really is not known—about nodular proliferation in humans and have deliberately avoided the controversial data in animals. As McNeal has emphasized,[5] there is substantial anatomic diversity among different species and none of the current animal models resemble the human prostate. For example, a dog's prostate is homogeneous, hyperplasia occurs uniformly throughout the gland and there are neither nodules nor the formation of new architecture that is so characteristic of BPH in humans.

The clinical management of BPH is, by comparison, relatively simple. The classic symptoms of obstruction are hesitancy on urination, a slow, often intermittent, urinary stream and a progressively smaller stream which ultimately responds to increased abdominal pressure by further diminution of its size and force. In 95% or more of cases with these symptoms, patients themselves, not the physicians, should determine whether their symptoms are sufficiently bothersome to warrant a surgical procedure. In about 60% of men with obstructive prostates, unstable bladders develop (spontaneous or provoked bladder contractions that cannot be suppressed)[6]; the symptoms of an unstable bladder are urinary frequency and urgency. Unfortunately, after surgical removal of the obstructive prostatic tissue, some 25% of unstable bladders remain unstable. Thus, a cautious physician will assure patients that whereas an operation will relieve them of a hesitant, poor and intermittent stream, the symptoms of frequency, urgency and nocturia may persist after operation in about 15% of men with obstructive prostates.

The issue of residual urine needs to be resolved. A postvoiding residual does *not* predispose a man to urinary tract infection unless, of course, bacteria are introduced

into the bladder by urethral catheterizations. Hasner dispelled this myth in 1962 by showing that the spontaneous infection rate was only 8.6% in 221 men with prostatic obstruction and residual urine of 50 ml or more[7]; the few patients who were spontaneously infected in the absence of catheterization were much older men with prolonged illnesses and 9 of the 19 had azotemia. If it is important to determine the amount of residual urine (which it rarely is), this can be estimated with ultrasound before and after voiding, or even by simple palpation of the bladder. Except for the rare case of a patient in whom an acontractile bladder develops from what is presumed (but not definitely known) to be secondary to long-standing obstruction and the occasional case of a patient who has azotemia from prostatic obstruction, there is little justification for concern over residual urine—and no justification for routinely catheterizing men to measure their residual urine as a gauge of the severity of their obstruction. If their symptoms of obstruction are sufficiently disturbing, they should have prostatectomy whether residual urine is present or absent. For these reasons, a careful history with attention to symptoms reflecting obstruction, a wise analysis of nonobstructive symptoms such as frequency and urgency, a single serum creatinine level and a gross examination for residual urine by either palpation or prevoiding and postvoiding pelvic ultrasonography are fully adequate to the task of helping a patient decide whether or not his symptoms warrant prostatectomy for benign prostatic hyperplasia.

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Case Reports

Kawasaki Syndrome in Office Pediatrics

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DRAMATIC MULTISYSTEM clinical features, involvement of the coronary arteries and absence of a known cause have stimulated considerable interest in Kawasaki syndrome among pediatricians during the past decade. It is a disease almost exclusively limited to children younger than 8 years and is associated with a case fatality of 1% to 2% due to coronary thrombosis or ruptured aneurysm.[1]

A review of published descriptions and case reports suggests that children with Kawasaki syndrome are either critically ill or appear to be in a severely toxic state and that all require admission to hospital.[2-5] This impression was challenged when two children with the syndrome were seen by one pediatrician in the first year of a new general practice. Both children were managed without hospital stay.

Reports of Cases

CASE 1. The patient, a 4-year-old child, was in good health before her presentation with a two-day history of fever and unilateral cervical swelling. On physical examination she had a temperature of 39°C (103°F). She appeared mildly ill and had erythema of the tonsils with a 3- by 5-cm tender right anterior cervical node. Erythromycin was prescribed. Five days later, her mother reported that the patient's eyes were "bloodshot" but she did not appear more ill. During the next week, she had right heel pain with a mild limp, malaise and anorexia while the fever remained low grade (37.8 to 38°C [100 to 101°F]). Examination 11 days after the onset of disease showed erythematous lips with cracking at the angles, resolution of the cervical adenopathy, mild edema and warmth without erythema over the lateral aspect of her right ankle. No pain was noted when the ankle was examined, though there was a mild limp. At this time the leukocyte count was 10,500 per μl with 64% polymorphonuclear cells, 31% lymphocytes, 3% monocytes and 2% eosinophils. The hematocrit was 33% and platelets were 545,000 per μl. The erythrocyte sedimentation rate was 102 mm per hour. X-ray examination of the ankles showed mild periarticular soft tissue swelling bilaterally. A throat culture was negative for group A *Streptococcus;* the streptozyme test for antistreptolysin O antibody and tests for antinuclear antibody and rheumatoid factor were negative; an electrocardiogram showed no abnormalities.

With an initial diagnosis of juvenile rheumatoid arthritis, treatment with aspirin, 5 grains every eight hours, was initiated. During the following week, there was resolution of the fever, red lips and limp as pronounced peeling of the palms and toes developed bilaterally without erythema or pain. The erythrocyte sedimentation rate was 50 mm an hour, leukocyte count was 9,400 per μl and the platelet count was 400,000 per μl. Kawasaki syndrome was suspected at this time and the aspirin dosage was decreased to 10 mg per kg of body weight a day. The skin lesion resolved after about one week. The following month the sedimentation rate was less than 20 mm an hour and the platelet count was normal; the aspirin therapy was then discontinued. Electrocardiograms continued to show no abnormalities and two-dimensional echocardiography showed normal coronary arteries. She remained well during the following year.

CASE 2. This 2-year-old male infant had been in excellent health until he was seen with a 24-hour history of fever to 40°C (104°F), "pink eyes" and a rash. On physical examination he appeared mildly to moderately ill and had a temperature of 39.4°C (103°F), bulbar conjunctival injection without discharge, nontender moderately enlarged cervical nodes and a generalized maculopapular erythematous rash, especially prominent on the face and trunk. He was sent home with a presumptive diagnosis of acute viral illness with exanthem and conjunctivitis.

During the subsequent five days, erythema of the palms and soles developed and there was persistent fever, malaise and anorexia. The rash became more intensely erythematous and spread to the extremities; the maculopapular pattern continued. A throat culture was negative for group A *Streptococcus*.

During the following week there was peeling of his fingers, toes and soles; his parents described an "awkward" gait. The fever and rash had gradually resolved. Examination showed nonerythematous desquamation of his distal fingers and toes and peeling of both soles. His gait was clumsy but without definite limp or ataxia. Examination of the joints showed no abnormalities. At this time, a leukocyte count was 12,400 per μl with 70% polymorphonuclear cells, 24% lymphocytes, 3% monocytes and 3% eosinophils. The hematocrit was 36% and platelets were 724,000 per μl. The erythro-

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cyte sedimentation rate was 81 mm an hour. Results of analysis of urine, chest x-ray examination and electrocardiogram were normal. Two-dimensional echocardiogram showed normal coronary arteries. He was given aspirin, 10 mg per kg a day.

During the next ten days, his appetite improved while the malaise and clumsy gait resolved. His skin was now normal. The platelet count was 425,000 per μl and erythrocyte sedimentation rate was 25 mm an hour. Aspirin therapy was continued for one more month until the platelet count and sedimentation rate returned to normal.

Discussion

In the initial report of Kawasaki syndrome in the English literature, Dr Tomisaku Kawasaki noted that the first case of what was then described as mucocutaneous lymph node syndrome was seen by him in 1961. In a survey of Japanese hospitals between 1964 and 1972, he and his colleagues collected 3,940 definite or suspected cases, all of which patients were, presumably, admitted to hospital.[6] An early report from the United States described 16 children from Hawaii who were admitted to hospital, all of whom were seen during a four-year period at the Kauikeolani Children's Hospital.[4] Other series of children requiring hospital care have emphasized the abrupt onset and febrile nature of the syndrome. A national survey of cases of Kawasaki syndrome in the United States showed that of 206 cases that met diagnostic criteria, 192 (93%) were in-hospital cases.[7]

Two epidemics of Kawasaki syndrome have been described, which suggests a wide spectrum of clinical severity when an entire community is investigated intensely. In eastern Massachusetts, 57 cases were reported during a three-month period; 51 (89%) of the children were admitted to hospital. In an epidemic of Kawasaki syndrome in Rochester, New York, 9 of 23 (39%) of the children required hospital care. Cases in both reports were ascertained by a review of hospital records, phone calls to physicians and media announcements. The study of these epidemics by the Centers for Disease Control allowed apparently less severe cases not requiring hospital treatment to surface.[8]

Kawasaki syndrome is seen primarily in children who experience a prolonged fever, usually lasting a week or more, associated with a nonspecific generalized erythematous rash and, on occasion, adenopathy. These signs would prevent a specific diagnosis if it were not associated with three others that, collectively, aid in the correct interpretation: (1) bulbar conjunctival injection without a discharge, (2) erythema of the lips followed by fissuring at the angles and crusting and (3) a striking erythema of the palms and soles associated with a more subtle induration of the dorsum of the hands and feet. Other focal organ involvement has been described less frequently (Table 1). Leukocytosis and an elevated erythrocyte sedimentation rate are found during the first week of the disease. Thrombocytosis is present in the second week and may last for more than a month. The elevated platelet count in association with a perivasculitis of the coronary arteries provides the environment for the development of coronary thrombosis and aneurysms in a few children who have Kawasaki syndrome.

TABLE 1.—*Diagnostic Criteria for Kawasaki Syndrome*

Major Criteria	*Characteristics and Associated Signs*
Fever	>5 Days
Conjunctival injection	Bulbar injection without a discharge
Erythema of lips	Followed by fissuring and crusting of lips Erythema of oropharynx Strawberry tongue
Induration of hands and feet; erythema of palms and soles	Desquamation of tips of fingers and toes 2 weeks after onset of fever followed by transverse grooves of fingernails 2 to 3 months later
Erythematous rash	Morbilliform maculopapular or urticarial
Enlarged lymph node	Variably present
Minor (Less Frequent) Findings	
Arthralgia and arthritis	
Diarrhea	
Abdominal pain	
Hepatitis	
Hydrops of the gallbladder	
Carditis	
Aseptic meningitis	
Laboratory Data	
Leukocytosis	
Thrombocytosis	
Elevated ESR	
Occasional findings	
Anemia	
Pyuria	
Pleocytosis	
Hypertransaminasemia	

ESR = erythrocyte sedimentation rate

The prolonged fever, rash and variable lymphadenopathy found in patients with Kawasaki syndrome can mimic many other, well-defined diseases familiar to office-based pediatricians. Kawasaki syndrome can easily masquerade as scarlet fever, Stevens-Johnson syndrome (erythema multiforme), a severe enterovirus infection or as an acute onset of a collagen vascular disease, especially Still's disease (juvenile rheumatoid arthritis). Infectious mononucleosis, serum sickness and leptospirosis have also been considered in the differential diagnosis.

The patient in the first case reported here appeared to have cervical adenitis when the initial presentation was limited to a tender, enlarged cervical node and fever. The bulbar conjunctivitis, rash, red lips and arthralgia unfolded gradually and undramatically. When the clinical pattern was pieced together at the end of the second week of illness, leukocytosis, thrombocytosis and an elevated sedimentation rate assisted in the confirmation of the correct diagnosis.

The second child had a more fulminant disease initiated by a high temperature, a generalized maculopapular rash, cervical adenopathy and bulbar conjunctivitis.

The initial clinical impression of viral infection with exanthem was challenged when the child's mother phoned the following day and reported the development of erythema of the palms and soles and a strawberry tongue. Desquamation of the palms, soles and fingers ten days after the initial examination in association with leukocytosis, thrombocytosis and an elevated erythrocyte sedimentation rate confirmed the diagnosis of Kawasaki syndrome.

Although both of these children had moderate malaise and anorexia during the acute phase of their illness, hospital admission was never considered necessary for either diagnostic, therapeutic or social purposes. The diagnosis of Kawasaki syndrome was apparent during the subacute phase in one patient and during the acute phase in the other. In retrospect, bulbar conjunctivitis without discharge and erythema of palms and soles were clues to the correct diagnosis early in the course of the disease when fever and rash were nonspecific presenting signs.

These two cases, which were both seen by one pediatrician in the first year of a new practice, occurred over a ten-month period. Although the children lived in the same region of an urban community, their socioeconomic status was different and they did not share preschools or play areas. A retrospective, informal survey of several group pediatric practices and a large health maintenance organization in the same community did not reveal a single case of Kawasaki syndrome without admission to hospital diagnosed during the same period of time. The number of children admitted to hospital with Kawasaki syndrome during this period of time was not higher than in previous years.

This report suggests that Kawasaki syndrome may be masquerading as other diagnoses in pediatric office practices. Careful examination of the conjunctiva, palms, soles and lips of young children who present with prolonged fever and a nonspecific generalized rash may lead to the discovery of many more patients with less severe forms of Kawasaki syndrome than previously reported. If this assumption is correct, the increased number of cases may provide clinical investigators with new clues to the cause of this elusive syndrome.

Summary

Published clinical, epidemiologic and laboratory data on Kawasaki syndrome have left primary care pediatricians with the impression that these children usually are acutely ill with a toxic presentation. Two cases from one general pediatric practice suggest that early symptoms and signs of this syndrome may be mild, atypical and resemble those of other, more common diseases. As coronary artery aneurysms and thrombosis may develop in children with variable expressions of Kawasaki syndrome, primary care pediatricians should be aware of the milder presentations that may be seen in an office practice.

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Community-Acquired *Pseudomonas aeruginosa* Pneumonia Associated With the Use of a Home Humidifier

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Pseudomonas aeruginosa is well recognized as a nosocomial pathogen. In an infection surveillance study at the Boston City Hospital in 1970, this organism accounted for 18% of postoperative wound infections, 17% of nosocomial lower respiratory tract infections and 11% of hospital-acquired urinary tract infections.[1] However, none of the community-acquired pneumonias or urinary tract infections in this study were due to *P aeruginosa*. In two prospective studies of cases of community-acquired pneumonia, Gram-negative bacteria were documented as the etiologic agents in 16%[2] and 20%[3] of cases. Of the 719 patients in these two studies, only 2 had *P aeruginosa* identified in their sputum specimens and none from blood specimens. When community-acquired *P aeruginosa* pneumonia does occur, it is usually in patients with severe underlying diseases or in parenteral drug abusers. Its occurrence in previously healthy persons is extremely rare.[4]

We report the case of a man with a 25-year history of asthma who had community-onset *P aeruginosa* pneumonia in an unusual epidemiologic setting. Other sources of community-onset *Pseudomonas* infections are discussed.

Report of a Case

A 39-year-old man presented to the emergency room with shortness of breath. Five days before admission he noticed the onset of cough productive of thick yel-

(Harris AA, Goodman L, Levin S: Community-acquired *Pseudomonas aeruginosa* pneumonia associated with the use of a home humidifier. West J Med 1984 Oct; 141:521-523)

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low sputum. For two days before admission he had had many episodes of rigors and drenching sweats. Pleuritic pain was localized to the left anterior thorax.

The patient's medical history included 25 years of asthma. During the several years before admission he had had severe symptoms year-round. Treatment was obtained at several outpatient clinics and emergency rooms. There were no hospital admissions during the 12 months preceding this admission. Medications included Tedral (a combination product containing ephedrine hydrochloride, phenobarbital and theophylline), Elixophyllin (theophylline), guaifenesin (Robitussin) and isoproterenol hydrochloride (Isuprel Mistometer). The patient had been using a home humidifier for the six months before admission.

On physical examination he was obviously chronically ill, asthenic and in acute respiratory distress. Temperature was 40.3°C (104.6°F) rectally, blood pressure 88/60 mm of mercury, pulse 140 per minute and regular and respiratory rate 40 per minute. Diffuse wheezes were present and breath sounds were decreased at the left base. The patient required emergency intubation and was transferred to the medical intensive care unit. Specimens of blood, urine and sputum were obtained for culture and were examined for the presence of aerobic and anaerobic bacteria and mycobacteria. Initial antibiotic therapy included ampicillin, gentamicin sulfate and clindamycin.

Laboratory data included a hemoglobin of 13.5 grams per dl with a hematocrit of 49%. The leukocyte count was 28,000 per μl. Arterial blood gas determinations done while the patient was breathing room air showed a partial oxygen pressure of 80 mm of mercury, a partial carbon dioxide pressure of 25 mm of mercury and a pH of 7.49. A chest x-ray study showed a left lower lobe infiltrate and small pleural effusion. A sputum Gram's stain showed heavy leukocytes with many Gram-negative rods. No intracellular organisms were seen. An acid-fast stain was negative.

Cultures of sputum, pleural fluid and blood specimens were positive for *P aeruginosa.* No other pathogen was identified. The patient's purified-protein derivative test was negative. Serum immunoglobulins and α_1-antitrypsin levels were normal. The antibiotic regimen was changed to carbenicillin (24 grams a day) and gentamicin (300 mg a day). On this regimen his condition slowly improved. His course was complicated by a bronchopleural fistula requiring surgical decortication. He was discharged from hospital 53 days after admission, having received antipseudomonad therapy for 46 days. Four months later he was readmitted to hospital with *Hemophilus influenzae* pneumonia. *P aeruginosa* was not present in his sputum at this time or 14 months later when he died of tuberculosis.

Discussion

The identification of *Pseudomonas aeruginosa* as the etiologic agent prompted a review of the patient's history for possible exposures. There were no recent admissions to hospital, antibiotic usage, parenteral drug use, trauma or use of whirlpool baths. However, for the past five months the patient had been using a home humidifier. The patient's home was visited three days after his admission to the hospital. The humidifier was in the bathtub, covered with dust and contained water. Cockroaches and fleas were observed both within the unit and on the surface. Cultures of the bathtub water trap, as well as the humidifier rim, plunger and water were all positive for *P aeruginosa.* All home and patient isolates had identical patterns of antibiotic sensitivities and pyocin typing.*

P aeruginosa has been isolated from 2% of pharyngeal cultures of persons not admitted to hospital.[5] Like other pseudomonads, this most common member of the Pseudomonadaceae is ubiquitous in water and moist soil. However, infection is seen in only a few unique settings. Outbreaks of *P aeruginosa* folliculitis and cellulitis have been linked to the use of whirlpools and hot tubs in various motels and spas.[6] Community-acquired endocarditis is most commonly seen in persons with heroin addiction where the organism may be transmitted by using contaminated syringes.[7]

P aeruginosa as a cause of community-acquired pneumonia is very rare.[1,2] When seen, it is usually in patients with cystic fibrosis or severe combined immunodeficiency syndrome and chronic granulomatous disease. *Staphylococcus aureus, Streptococcus pneumoniae* and *H influenzae* are frequent antecedent pathogens before colonization and infection with pseudomonads, which are usually mucoid and nontypable. Recurrent and ongoing courses of antibiotics and the use of home humidifiers are frequently a part of the therapeutic regimen of these patients. Our patient had none of the predisposing diseases associated with community infection with *P aeruginosa* but had frequently used a humidifier.

Contaminated anesthesia machines, mechanical ventilators, inhalation therapy equipment, delivery room resuscitators and humidifiers have all been implicated in hospital-acquired respiratory tract diseases.[8,9] Humidification connotes the addition of moisture to the air without production of aerosols. Portable humidifiers with a spinning disc, similar to that used by our patient, are more appropriately considered fine-particle-reservoir nebulizers and have been a source of *P aeruginosa* pulmonary infections in hospital.[10] Their home use has been associated with fungal aerosols, hypersensitivity pneumonitis and asthma.[11] However, no community-acquired cases of Gram-negative pneumonia have previously been traced to a contaminated respiratory device in the home. Unlike other home respiratory devices, patients do not come in direct contact with humidifiers of this type. Coupled with the ubiquitousness of *P aeruginosa* in water, its presence in the bathtub water trap of our patient and the absence of clinical conditions known to be associated with colonization with pseudomonads, it is far more likely

*Pyocin typing was done by H. Griebel, MD, and T. Bird, PhD.

that a contaminated machine led to colonization and subsequent infection in our patient than that the infected patient directly contaminated his machine.

Maintenance of our patient's humidifier was certainly substandard. Stagnation of water for long periods of time would permit a pronounced increase in colony counts available for aerosolization. Respiratory devices such as the one used by our patient are used for "humidification" in hospitals and homes throughout the country without proved therapeutic efficacy. When efficacy is questionable, utter safety becomes the overriding concern. Patients such as ours point up the possibility for a rare but potentially life-threatening complication. We suggest that if these portable home humidifiers are used, patients should be instructed to discard residual water after each use, dust and rinse thoroughly before use after storage and only fill with water just prior to usage.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Why Celsius?

TO THE EDITOR: Despite the national trend toward adoption of the metric system, practicing physicians have been slow to conform. We believe that most clinicians do not favor conversion to the metric unit of temperature (Celsius), and that the Fahrenheit scale may be a superior measurement tool.

The need for a worldwide measurement system was recognized more than 300 years ago by Gabriel Mouton. Participation in the international measurement language has many practical advantages in both the scientific and economic communities.[1] The Secretary of Commerce recommended in 1971 that the United States convert to the predominant use of the metric system. In response, Congress enacted the Metric Conversion Act of 1975.

The metric system has been introduced as a "package deal" to the US scientific community. In medicine, authors and practitioners have been encouraged to adopt the metric system in the literature and practice of medicine. More than 150 biomedical journals have agreed to receive manuscripts prepared in accordance with requirements set forth by the International Committee of Medical Journal Editors. These requirements specify that "Temperatures should be given in degrees Celsius."[2] A recent article rated medical journals read by family physician educators.[3] Nine of these ten journals have requirements for units of measurement. Of these, three require that units of temperature be presented in Celsius only, four require that Celsius be given initially followed by Fahrenheit units in parentheses (the policy of *The Western Journal of Medicine*), one accepts only Fahrenheit and the *New England Journal of Medicine* leaves the decision regarding temperature units to the authors (the only journal doing so).

Clinicians appear less ready to convert to Celsius. To help understand the sentiments of the medical community regarding this issue, we carried out a survey of 62 family physicians in the Seattle area. Completed questionnaires were received from 57 of 62 (92%), including faculty and fellows at the University of Washington (19), residents at the University of Washington (14) and physicians at a large health maintenance organization (24). Only eight respondents had received medical training in hospitals where Celsius was the standard unit of measurement, and the mean number of years in practice was 9.8. Of all respondents, 36% felt that Fahrenheit was a more clinically useful measurement, 9% felt that Celsius was more useful and 55% felt that the two were equally useful. As part of the survey, we asked for Celsius equivalents of two clinically meaningful Fahrenheit temperatures: In estimating the Celsius equivalent of 100°F (low-grade fever), 95% of respondents were within 0.3°C of 37.8°C. In estimating the Celsius equivalent of 104°F (high fever), 65% of respondents were within 0.3°C of 40.0°C. There was no relationship between years in practice and accuracy of estimation. Respondents who favored °F or who felt that °F and °C were equally useful were more likely to be accurate in their metric estimates of 104°F than those who favored °C (Table 1).

TABLE 1.—*Relationship Between Perception of Clinical Utility (°C versus °F) and Accuracy of °C Estimate of 104°F (N = 54)*

	Accuracy of °C Estimate of 104°F	
	Estimate ≤.3°C	*Estimate >.3°C*
°F felt to be more clinically useful or °F and °C perceived to be equally useful	36 (73%)	13 (27%)
°C felt to be more clinically useful	1 (20%)	4 (80%)

P .06 (2-tail, Fisher's exact test)

The data in our small study show that (1) more than 90% of respondents felt either that °F was a more clinically useful measurement or that °F and °C were equally useful; (2) in general, respondents were quite accurate in their estimates of metric equivalents of 100°F and 104°F and (3) there was no evidence that those favoring Fahrenheit were less knowledgeable about metric equivalents than those favoring Celsius.

If the practicing medical community is resisting the conversion from Fahrenheit to Celsius, perhaps it is not out of "laziness" or "old habits." There are 40 decimal increments between 100°F and 104°F. Between the metric equivalents there are 22 decimal increments. Perhaps resistance to change is due to an understanding that the Fahrenheit scale is, in the words of Arnold L. Smith, "the more sensitive, expanded scale instrument."[4]

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Potency of Synthroid Tablets

To the Editor: The artiele "Maintenanee Requirements of L-Thyroxine in the Treatment of Hypothyroidism" by W.A. Kehoe, B.J. Dong and F.S. Greenspan,[1] in the June 1984 issue, eontains an addendum whieh has some ineorreet statements that may be misleading to your readers.

The addendum states that Synthroid tablets were reformulated in 1983. In fâct, the reformulation took place in 1982. Flint Laboratories' studies show that the bioavailability of the reformulated tablets averages 74%, compared to 70% for the old formulation. The figures of 78% and 100% given in the addendum are aetually those reported not for bioavailability but for poteney by Stoffer and Szpunar.[2] These poteney estimates were, however, based on immunoassay, a teehnique that has not been validated for measurement of tablet poteney. When official USP methodology is used, the poteney of Synthroid tablets has not ehanged with the reformulation.

I hope this will elarify matters for your readers.

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* * *

Drs Kehoe, Dong and Greenspan Reply

To the Editor: We are grateful to Dr Horwitz for formally announcing that their produet was reformulated in 1982. We are also pleased to know that it is not the bioavailability that has been ehanged, although L-thyroxine absorption is very variable.[1-3] However, our clinical experienee in 1983-84 of inereased biologie potency in patients previously maintained on a stable dose of L-thyroxine is similar to that observed by *Medical Letter* endoerinology consultants[4] and tends to agree with the findings reported by Sawin and eo-workers[5] and Stoffer and assoeiates.[6] Sawin and co-workers noted that the aetual content of Synthroid tablets prior to reformulation eontained 20% to 30% less than their stated eontent as measured by radioimmunoassay while Synthroid after reformulation eontained 100% of the stated amount.[6] Interestingly, both studies were able to correlate the deereased tablet eontent with decreased response as measured by thyroid funetion tests.

We do not understand why there should be signifieant discrepancy in measuring tablet eontent between high-pressure liquid chromatography (HPLC) and radioimmunoassay but caution that patients previously maintained on a stable dose of L-thyroxine (Synthroid manufactured prior to 1982) may need readjustment of their dose downward to avoid clinical toxicity when receiving the newly reformulated L-thyroxine tablets.

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The Effect of Heparin Dilution on Arterial Blood Gas Analysis

To the Editor: Drs Dake, Peters and Teague[1] reeently published an informative letter about artifacts in arterial blood gas measurements due to dilution with heparin solution. Their information agrees with data published by Dr James Hansen and me,[2] but there are points whieh I disagree with or wish to clarify.

Adding heparin solution to blood dilutes plasma earbonie acid (H_2CO_3) and, therefore, earbon dioxide; the measured carbon dioxide pressure (P_{CO_2}) then will deerease in proportion to the amount of dilution, as the authors state. I disagree that "when exeessive amounts of heparin are added . . . Pa_{CO_2} [arterial earbon dioxide pressure] is the measurement most profoundly affeeted," beeause eoneentrations of bicarbonate and base exeess deerease proportionately with P_{CO_2}. Equal dilution of P_{CO_2} and biearbonate accounts for the fact that pH is unaffeeted, as the authors report. These dilutions ehange the "metabolie" and "respiratory" components of aeid-base measurements proportionately, aeeounting for elinieally unexplained stimultaneous mild primary respiratory alkalosis and primary metabolie acidosis. I agree that pH is also not affeeted measurably by adding aeidie heparin, since the buffering capacity of heparin solution is mueh less than that of blood.

I disagree on two other points. I think it is ineorreet to state that "the partial pressure of a gas in solution is proportional to the solubility coefficient of the gas and the partial pressure of the gas overlying the liquid." The partial pressure of a gas in solution is the same as the partial pressure of the gas overlying the liquid following equilibration. The solubility coefficient could affeet partial pressure only indireetly if the gas dissolved signifieantly, deereasing the amount and partial pressure of the gas overlying the liquid. In the ease of CO_2 this would be at most only a miniseule faetor.

However, with the high "solubility coeffieient" of oxygen in blood, dilution could have a significant effeet on measured oxygen pressure (P_{O_2}). We found this effeet to be somewhat different from that reported by Dake and eo-workers. Unpublished data from our laboratory suggest that the effect of

dilution on Po_2 is predictably very small to very large, depending on partial pressures of oxygen in blood and heparin solution and the dilution. Heparin solution in an unused bottle will normally have a Po_2 of 150 mm of mercury, the same as in air with which it equilibrates. Dilution would therefore raise blood Po_2 if it were originally less than 150 and would lower it if it were greater than 150. Interestingly, we found the absolute pressure of gas in heparin bottles after they have been used was as high as 4 atm (Po_2 approximately 600 mm of mercury) because of the common practice of pumping more air back into the bottle than the volume of solution removed, making the measured blood Po_2 erroneously high. The magnitude of the error depends on the Po_2 of blood and solution and the amount of dilution. If the Po_2 and oxygen saturation of the blood are high and the slope of the oxyhemoglobin dissociation curve is low, "dissolving" oxygen from the gas phase raises Po_2 considerably. An undiluted blood Po_2 of 120 mm of mercury increased to 200 when the blood was diluted 30% by heparin solution with a Po_2 of 400. In contrast, when blood Po_2 and oxygen saturation are low and the slope of the oxyhemoglobin dissociation curve is high, measured Po_2 is affected less. An undiluted blood Po_2 of 50 mm of mercury increased to 58 with the same heparin Po_2 of 400 and 30% dilution. With average pressure in the heparin bottle and average dilution, when blood Po_2 was less than 60, dilution artifacts were small, only rarely exceeding 3 or 4 mm of mercury. When arterial Po_2 was over 100, dilution artifacts were 10 to 15 mm of mercury. Therefore, whatever the initial conditions, the effect of the gas phase and solution Po_2s on measured blood Po_2 would usually not be clinically significant.

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* * *

Dr Dake Replies

To the Editor: We appreciate Dr Simmons' comments which help to clarify and expand points discussed in our prior correspondence.

In stressing the effects of heparin overdilution on the major blood gas measurements of clinical interest directly measured by automated blood gas analyzers (that is, pH, arterial oxygen pressure [Pao_2] and arterial carbon dioxide pressure [$Paco_2$]), we did not address changes in machine calculated values for base excess and bicarbonate.

Indeed, the dilution of arterial blood samples with large amounts of heparin solution will have an effect on base excess and bicarbonate directly proportionate to the decrease in $Paco_2$. Of all the variables examined, however, it is the effect on $Paco_2$ which has the most potential clinical significance.[1-3]

Also, we thank Dr Simmons for sharing data from his laboratory regarding the partial pressure of oxygen in heparin bottles and its effect on the Pao_2 of arterial blood specimens.

Bageant[2] and others have previously described the changes in Po_2 resulting from pumping air into heparin bottles—however, their results and data from our laboratory differ from Dr Simmons' observations in the magnitude of the effect and the potential for clinical importance.

We repeatedly pumped air into different-sized bottles containing heparin solution until a precariously conspicuous bulge was produced in the rubber top. Despite this maneuver designed to produce pressures exceeding those developed during repeated routine clinical use, the maximal heparin solution Po_2 recorded was 244 mm of mercury. In a similar manner, by pushing extra air into a heparin bottle Bageant[2] forced the Po_2 to 275 mm of mercury; however, both these values are far below the Po_2 of "approximately 600 mm of mercury" Simmons found in "heparin bottles after they have been used."

Both Bageant[2] and our laboratory found essentially no difference between the Pao_2 of blood specimens obtained using a minimum of heparin solution equilibrated with ambient pressure and heparin solution from a bottle with positive pressure following repeated air injection.

In summary, despite any differences regarding minor points, there is general agreement that strict adherence to recommended sampling techniques is required to ensure consistently accurate arterial blood gas analysis; this includes utilizing a minimum amount of heparin solution.

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More on Poison Oak Dermatitis

To the Editor: It is sad to be reminded that some physicians reject new forms of therapy without attempting to determine whether they would allow their patients to be better served. The potential loss to their patients is magnified if the proposed therapy is not only pleasant and safe, but also without significant cost and so effective that it minimizes both the need for prescription medications and the number of visits to physicians' offices. Hot soapless showers in the treatment of poison oak dermatitis[1] seem to be a form of therapy with these advantages.

Their letters[2-4] suggest that Drs Drake, Tromovitch, Stegman, Glogau and Gross have never suggested this technique to any of their patients. I would encourage them to do so before rejecting the treatments as being either inappropriate or useless.

Drs Tromovitch, Stegman and Glogau expressed several concerns including a possible need to specify precise water temperatures. In practice, this precision has not been necessary. None of my patients carry a thermometer into their shower, but rather test the water temperature by hand as they enter in order to assure their safety. Patients have usually found that "comfortably hot" water (obviously warmer than tepid water) gives therapy that is more pleasant than cooler treatments and probably results

in a longer residual pruritus-free interval. Without the use of soap, postshower dryness of the skin has not been encountered.

My experience with orally given prednisone is apparently similar to theirs. Corticosteroids are very effective medications for blunting the severity of rhus dermatitis, but take several days to become fully effective, and occasionally patients report insomnia, indigestion or feelings of unreality while using them, which they find to be more objectionable than their dermatitis or more inconvenient than their comfortably hot showers. Most patients with severe enough dermatitis to justify the use of corticosteroids have found showers to give substantial additional relief while waiting for their medication to become effective.

Dr Gross apparently was upset by my letter and failed to read it carefully. His considerable concern about the dangers of hot bathing are shared by most physicians, and his experience with hot soaks is similar to my own. Hot bathing was not, of course, the therapy which was proposed for poison oak dermatitis. If used for treating this disorder, hot baths would not only carry significantly greater risk but would also be both more time-consuming and more difficult to apply to some areas such as a protuberant abdominal wall.

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Herpes Zoster Neuralgia

To the Editor: The letter by Samuel Ayres, Jr,[1] in the February 1984 issue regarding the treatments of herpes zoster neuralgia is, of course, of great interest. However, it is noted that his treatment refers to a paper published in 1973. It would be interesting to know what his experiences have been in the ensuing ten years. Also, in regard to the letter on the same subject by Marvin E. Engel,[2] I am wondering if there is any study that would support the assertion that the intralesional injections of triamcinolone is any more efficacious than the systemic effects. In other words, the dosage he recommends would be bound to give systemic effects, and unless some type of controlled study was done, one would not be able to determine whether intralesional is a preferred route.

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Topics in Primary Care Medicine

Benign Prostatic Hyperplasia

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Benign prostatic hyperplasia (BPH) is a nearly ubiquitous condition in elderly men. Symptoms attributable to BPH are increasingly common after the fifth decade and account for a significant percent of the urologic complaints confronting primary care physicians. It is essential that primary care physicians be familiar with the principles of evaluation and management of this important problem.

Anatomy and Physiology

The prostate is a pyramidal-shaped fibromuscular and glandular accessory sex organ that lies retroperitoneally encircling the bladder neck. It is composed of two distinct types of glandular elements—the inner periurethral glands, which are responsible for the hyperplasia of BPH, and the external glands, which are the site of neoplastic degeneration. The secretions (seminal plasma) of the prostate and other sex accessory glands (epididymis, vas deferens and seminal vesicles) constitute most of the volume and chemical components of the ejaculate. This fluid has a high concentration of zinc, potassium, citric acid, fructose and prostaglandins and contains a variety of proteins including proteolytic enzymes and immunoglobulins. These substances are thought to provide optimal conditions for sperm motility and survival in the male and female reproductive tracts, and probably also play a role in protecting the male genitourinary tract from infection.

Incidence

Autopsy studies of men older than 40 years have found an incidence of BPH of 80%. By the eighth decade, 90% of men will have BPH and it is estimated that 10% of men who live to age 80 will require an operation for BPH. No association of BPH has been found with social class, marital state, celibacy, sexual drive or blood groups. However, symptoms develop in men with European heritage more often than in men with Asian heritage. Associations with coronary artery disease, hypertension, diabetes mellitus and cirrhosis are postulated but no common etiologic factors have been identified. Whether or not men with BPH are at increased risk for cancer of the prostate has not been determined.

Pathophysiology of BPH

Periurethral glandular hyperplasia begins after 40. As the volume of tissue in the periurethral gland increases, the external glands and the urethra become compressed. Abundant growth of the periurethral gland can occasionally result in urethral obstruction even without detectable enlargement on a rectal examination. The pathogenesis of BPH has been extensively studied and recently reviewed. Current theory holds that BPH results from an age-related increase in the serum ratio of estrogens to androgens and a concomitant increase in the dihydrotestosterone content of the gland. These hormonal changes are thought to act synergistically in susceptible glands to cause hyperplasia. The importance of testosterone and its derivatives in the pathogenesis of BPH is supported by a total absence of BPH in eunuchs and regression of BPH following castration.

Enlargement of the prostate without obstruction causes no obvious physiologic derangements. The major consequences of BPH result from the pressure effects of urethral obstruction on the bladder, ureter and kidneys. The initial response of the bladder to outlet obstruction is detrusor muscle hypertrophy. This hypertrophy generally remains clinically silent because the increased bladder contractility is able to overcome the outflow resistance. Progressive outlet obstruction results in further increases in intravesicular pressure with herniation of bladder mucosa between the trabeculated muscle bands producing sacculations and eventually diverticula. Unchecked, this process eventually leads to in-

(Cygan R, Rucker L: Benign prostatic hyperplasia [Topics in Primary Care Medicine]. West J Med 1984 Oct; 141:528-530)

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ABBREVIATIONS USED IN TEXT

BPH = benign prostatic hyperplasia
IVP = intravenous pyelogram

complete bladder emptying, progressive dilation, interference with ureteral emptying and disturbance of the ureterovesical valve mechanism. Dilation of the ureter and renal pelvis follows and can result in progressive renal insufficiency, tubular concentrating defects, hypertension and hyperkalemic distal renal tubular acidosis.

Clinical Features

Disturbances of micturition are the predominant presenting symptoms of patients with symptomatic BPH. A patient may complain of diminution in the caliber and force of the urinary stream, hesitancy in initiating voiding (especially on arising in the morning), a feeling of incomplete emptying of the bladder, frequency or nocturia. Because residual bladder urine and bladder diverticula predispose to cystitis and recurrent urinary tract infections, symptoms of lower or upper urinary tract infection may predominate. With bladder decompensation, symptoms of overflow incontinence occur. The dilated veins on the surface of the enlarged prostate are subject to rupture with resultant gross or microscopic hematuria.

On occasion, BPH remains clinically silent until nonurologic symptoms bring the patient to medical attention. Patients may present with gastrointestinal symptoms due to massively distended bladders or hydronephrotic kidneys. Alternatively, weight loss, weakness, mental confusion, cardiac decompensation or anemia from advancing renal failure may develop even in the absence of severe disturbances in micturition. This mode of presentation for BPH has been referred to as "silent prostatism." Finally, patients may present with acute urinary retention. Such episodes may be precipitated by enforced bed rest, vigorous use of diuretics, an alcohol binge or the injudicious prescription of anticholinergics, major tranquilizers, tricyclic antidepressants or decongestants. Aminophylline (theophylline and ethylenediamine), the antiarrhythmic disopyramide phosphate and cimetidine are recent important additions to the list of drugs capable of precipitating acute urinary retention.

Differential Diagnosis

The type of diseases that should be considered in the differential diagnosis of BPH, of course, depends on a patient's presenting complaints. Purely obstructive symptoms (decreased force of stream, hesitancy) may be seen with urethral strieture and prostatic carcinoma. Irritative symptoms (urgency, burning, penile pain) often coexist with obstructive symptoms and occur with acute and chronic prostatitis, cystitis and bladder cancer. Neurogenic bladder dysfunction can result in incontinence and urgency (spastic bladder) or incontinence and urinary retention (flaccid bladder). Hematuria should raise the suspicion of both lower and upper tract cancer.

Diagnostic Evaluation

Evaluation of any of the above complaints should include initial observation of a patient's voiding to substantiate any pronounced decrease in the size or force of the urinary stream. This should be followed by an examination of the lower abdomen and flanks for evidence of enlarged kidneys or bladder distention and a careful rectal examination. Using a well-lubricated gloved index finger with the patient in the knee-chest position or leaning forward over an examining table, the prostate should be carefully examined. A normal adult prostate is chestnut-sized, firm and elastic with the consistency of a rubber ball. Its lateral margins should be distinct, and a shallow, median furrow is usually palpable. Hyperplasia usually produces a smooth, firm elastic enlargement of the prostate. Stoney hard, asymmetric or nodular prostates are more likely to harbor cancer. A digital rectal examination has been shown to be as sensitive and specific as the more costly noninvasive techniques for detecting clinically apparent cancer in a hypertrophic prostate gland. A point that deserves emphasis is the inconsistent relationship between prostatic size and degree of obstruction. Normal-sized glands can cause severe obstruction when periurethral hyperplasia predominates, whereas huge glands do not invariably cause obstruction. Straight catheterization after voiding can also be done to assess bladder function. A post-voiding residual of greater than 50 to 100 ml of urine is abnormal and suggests significant obstruction or bladder decompensation (or both). Analysis of urine should be done to assess concomitant infection, presence of hematuria and the renal concentrating ability. Blood urea nitrogen and serum creatinine levels should be measured to evaluate renal function. An intravenous pyelogram (IVP) was once considered a routine part of the workup of patients with possible BPH. This practice has recently come under critical review and it now seems more reasonable to do an IVP only in those patients whose history or results of a physical examination or laboratory tests indicate the possibility of significant associated urinary tract abnormalities. For example, an IVP should be done if hematuria or disproportionate renal insufficiency is present. Renal ultrasonography can be done when radiographic contrast materials are contraindicated. If there is a suggestion of neurogenic bladder dysfunction, a cystometrogram is mandatory. Cystoscopy should be carried out on all patients who require prostatectomy and is best done immediately before the surgical procedure.

Management

Management options should be influenced by both the subjective severity of symptoms and the objective assessment of severity of obstruction. Many patients with mild symptoms and minimal evidence of significant obstruction can be managed conservatively. Most of these patients will show spontaneous fluctuations of symptoms for years with stable renal function, and a period of observation is justified in this group. Taking an extra minute or two to fully empty the bladder may provide symptomatic relief for some patients. Avoiding diuretics before bedtime, including alcohol and caffeine, may diminish nocturia and prevent nocturnal bladder distention. Drugs that interfere with bladder contractility should be used judiciously. The use of hormonal therapy (progestins and antiandrogens) for treating symptomatic BPH is still under investigation. α-Blocking drugs such as phenoxybenzamine hydrochloride and prazosin hydrochloride may also afford symptomatic relief by de-

creasing α-adrenergic-mediated increases in bladder neck and urethral muscle tone. Postural hypotension and dizziness are limiting their more widespread use, however.

Surgical intervention is clearly indicated for those patients whose severe obstruction has led to evidence of deterioration of bladder function (large postvoiding residuals, recurrent infections or acute retention) or renal function (rising urea nitrogen and creatinine levels, evidence of hydronephrosis or distal renal tubular acidosis). The few patients who are disabled by their symptoms but are without evidence of severe obstruction need careful evaluation by a urologist to determine if a surgical procedure might relieve their symptoms. Urine flow measurements may be useful in assessing the presence of significant obstruction in these patients. The choice of the surgical procedure will depend on the size of the prostate, the need to treat accompanying problems such as bladder diverticula and the experience of the surgeon. Transurethral resection of the prostate is the most common surgical approach and most patients can be effectively treated by this method. Suprapubic or retropubic approaches are used when a prostate is large. The overall mortality for simple prostatectomy is less than 1%. In patients with poor general health, advanced cardiopulmonary disease or uremia (or a combination of these), the operative mortality increases to about 5%. Morbidity is seen in about 15% to 20% of cases and includes bleeding, infection, incontinence, stricture, retrograde ejaculation and impotence. Those few patients who are deemed inoperable or who refuse an operation can be managed with intermittent or ongoing Foley catheter drainage.

The vast majority of carefully selected surgical patients will have complete relief of symptoms postoperatively. Persistence of symptoms usually implies the presence of concomitant problems that escaped detection preoperatively. Recurrence of BPH occurs about 5% of the time in the first ten years following transurethral resection of the prostate. The continuing risk of prostatic carcinoma in residual prostatic tissue should be kept in mind.

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Informed Opinion

A Clinician Looks at Health Planning

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The purpose of this paper is to encourage physicians to use their clinical thinking in a leadership role—advising, interpreting and innovating—in the presently evolving health planning. As with the successful practice of medicine, where clinical thinking involves translating the medical needs of the patient into a language the patient understands rather than simply prescribing a course of therapy, so successful health planning needs careful and detailed interpretation by the physician to the public rather than a prescribed course of action concerning particular institutions or public policy. Now that federal health planning is being decentralized, there is a unique opportunity for physicians to replace previous politically polarized attitudes with a powerful means for constructive change, clinical thinking, the dispassionate judgment of what is best for the patient, based on medical knowledge and experience.

Future Trends

Though national health planning disappoints most concerned observers, significant improvement is possible. There is the strong possibility that we are entering a "self-service society," where local volunteers will enhance and develop a new type of functional health planning system as an extension of grass roots politics. Many more concerned and informed consumers can be expected to enter and sustain health planning, now in their own way, perhaps even making it a potent community instrument. Nathan Glazer has noted, "Between 1965 and 1971, according to the Department of Labor, the number of Americans doing volunteer work increased from 22,000,000 to 37,000,000, a trend which appears to be accelerating."[1(p88)]

A second driving force for change is the inexorable pressure of technological innovation, which delivers ever-increasing specialized intense medical service to fewer and fewer people, apparently at the expense of the poor and the disenfranchised, preventing, and lately even jeopardizing, general hospital services. (At present, coronary artery bypass surgery, serving 0.04% of the nation's population, accounts for 1% of the nation's health bills. The end-stage renal disease program, serving less than 0.25% of all medicare part B beneficiaries, accounts for more than 9% of medicare expenditure.[2]) The present failure of health planning to articulate the broad implications of health care allocation can be expected to change as explicit medical care rationing is forced upon the nation. The balance between curative medicine and prevention and between low tech medicine and high tech medicine demands a rational forum in which neither is neglected and both are encouraged, despite the state of financial triage. The need for clinical thinking increases as health planning, willy-nilly, is forced to cope with these vast problems.

Past Trends

The following example should clarify a chronic pitfall physicians have fallen into when failing to apply clinical thinking to the body politic. While proposing legislation altering the configuration of state health planning to more closely reflect present needs, Oregon's chief state health planning administrator was invited by the state medical association's Subcommittee on Public Policy for a dinner meeting of "informal" talk. Since he wished to secure input from the physicians, as well as share the reason for proposed changes, he agreed, but he found himself alone with six doctors and two hospital administrators who spent the evening lecturing him on "the demeaning, insinuating and inflammatory language" of the proposed bill. This was done after the medical association had already established its policy, strongly disapproving the legislation. The next morning the chairman of the subcommittee apologized by telephone for what had happened, but by then the damage was done. It is unlikely that any member of that subcommittee in practicing medicine would lecture patients about "demeaning, insinuating and inflammatory language" as part of a therapeutic program; yet, when treating the body politic, one and all abandoned their sound clinical thinking. Certainly, none extended their clinical philosophy in keeping with the American Medical Association's policy that calls for voluntary health planning as a collaborative community effort to develop and use health resources in an orderly fashion.

(Crawshaw R: A clinician looks at health planning [Informed Opinion]. West J Med 1984 Oct; 141:531-533)

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ABBREVIATIONS USED IN TEXT

SHCC = Statewide Health Coordinating Council
SHPDA = State Health Planning Development Agency

The Process

The extension of clinical thinking to health planning is not so complex that most physicians cannot intuitively appreciate it. First, a diagnosis is established. Then, a consideration of alternative therapeutic approaches, which carefully evaluates the patient's resources, is undertaken and shared with the patient in an understandable fashion, followed by an ongoing, collaborative effort to correct the pathologic condition.

Much of the present difficulty in treating the body politic does not arise out of the diagnosis, but from the new and complex languages which seriously interfere with the physicians' communication and collaboration in considering therapeutic alternatives. For example, in the past when a community needed a new service—a burn center, for example—it was relatively easy for the physicians to make the case in a language that was understandable to most thinking citizens, and after a period of deliberation and fund raising, the medical resource would be established. Now, because of the involved nature of medical care, cost increases, burgeoning technology and an aging and more demanding public, now called "consumers," physicians are faced with a confusing situation in which there are a number of "new" experts with their own language. Despite this proliferation of tongues and complexity of fulfillment, physicians' most powerful tool for constructive change remains, clinically thinking, "What is best for the patient?"

The Oregon Statewide Health Coordinating Council (SHCC—pronounced "shick") serves as an example of the unavoidable complexity that accompanies clinical thinking in a public arena. Like presently evolving boards of hospitals, medical licensure, professional standards review organizations, business and labor health coalitions and boards of health, the SHCC has consumer representation; in fact, a majority are consumers. No longer is it possible for a physician to simply lay out the "diagnosis" for health planning to the 30 members of SHCC and expect direct implementation of the medical profession's treatment plan. Nor is it enough for the physician to simply sit back and criticize or ridicule the plans of others. Clinical thinking must now be translated into citizens' language in open, sometimes contentious, "town hall" meetings.

The Languages

The consequent forum created within SHCC has three prime cohorts: planners, consumers and providers—each with interests arising from different areas, with different mind sets and, consequently, with different languages. Planners from the State Health Planning and Development Agency (SHPDA) are trained in the arcane language of political science, government regulation and statistics. They are paid by the government to monitor and control the health delivery systems through academic principles of rational allocation of health resources. They speak "bureaucratese." The providers, though a polyglot crowd, are dominated by physicians who are trained in an even more arcane language of scientific medicine, "medicalese." The providers are seen as intent on following health planning along idiosyncratic practice styles which are frequently labeled as favoring their income and political self-interest. The third group, the consumers, the most heterogeneous, are not paid for their involvement in health care planning. In fact, consumers are frequently preoccupied with how much everyone else is being paid in the mounting cost of the entire enterprise. Consumers speak a language of personal experience with health care delivery, "pain and suffering," which they hope proves useful by encouraging relevant community action.

Of the three languages, "pain and suffering," the most difficult to articulate, is easily the most dramatically powerful. Should a President suffer from poliomyelitis, or have a close relative who is mentally retarded, forthwith the nation will have a formidable federal program to alleviate or eliminate that particular condition. Any doubts about Congress supporting end-stage renal dialysis were resolved in 1971 when the vice president of the National Association of Patients on Hemodialysis was dialyzed before the House Ways and Means Committee, blatant "pain and suffering" talk where it counts.

Patently, SHCC consumer members lack the political "eloquence" to articulate their pain and suffering as clearly as Presidents do. They are generally diffident and are more likely to speak "pain and suffering" in the bytalk of the SHCC meetings, during coffee breaks, confiding their concern about a husband committed to a state hospital, a child dying of leukemia, the neglect a fellow member of a minority has suffered, the need for an ambulance service in their rural area or all too often their outrage at mounting personal health insurance bills. They concur on the ultimate goal of health planning—equitable allocation of resources—but too often SHCC consumer members lack the means of translating their "pain and suffering" into the technical jargon of statistics and regulations. Understandably, the failure to translate their concepts of health planning into action leads to considerable frustration, as well as enforced dependence on health providers to speak for them. Their frustration was eloquently voiced when a consumer member of SHCC said, "I joined this outfit a number of years ago to find out what is really going on in health care, and we are still chasing government regulations. It is time we turned over a few rocks and see what crawls out."

The Clinical Dynamic

The impact of these three languages on SHCC has been a three-way dynamic fluctuating from shrill power confrontations to harmonious negotiations. The dy-

namic had been anticipated by the framers of the original federal legislation who, suspicious that the providers would dominate planning, mandated a consumer majority for SHCC. The government's suspicion of providers is matched by the providers' unrelieved mistrust of the government. Its regulations are seen as intentionally stacked against providers, pitting them against consumers, in order to give the government a free hand for its own plans. Not surprisingly, any proposal originating with the planning establishment, the SHPDA, has been reflexly greeted with provider cries of "Pure ignorance of the real situation!"

Predictably, consumers initially felt outclassed in the babel of two unfamiliar languages, and sometimes voted with their feet. However, with diligence and careful attention, consumers have come to understand the power of their own language, "pain and suffering," particularly when courted for votes by one or another of the other two factions.

The fact that each cohort has its own mind set and language should not be construed to mean that coherence and agreement exist within cohorts, no more than it should be expected that all who speak English will agree. Planners at the SHPDA level have been at sharp odds with Health Service Agency planners about Certificate of Need decisions, consumers interested in antifluoridation have not hidden their displeasure with parent groups pressing for school administration of fluorides, and among the providers the dissension between the fee-for-service and health maintenance organization physicians has at times almost disrupted SHCC meetings. Such disagreements within cohorts are natural and expected, and though generating hard feelings and grudges, the internal dissensions have not destroyed the original commonality of purpose. The flaw of health planning occurs in the continuing, vast discord among three cohorts, each with its individual language, and the difficulty in developing the harmony necessary for relevant community action.

Results

As deep changes continue to shake existing planning institutions, the polyglot language of health planning should shift from national "bureaucratese" towards local "pain and suffering." It is then that "medicalese" based on extended clinical thinking has a unique potential for framing questions and translating ideas into the commonly understood language of constructive action. The recent economic recession presented the SHCC with such an opportunity. With unemployment rates high, approximately 300,000 Oregonians were without health insurance coverage. SHCC took a long hard look at a real and present problem not covered by federal regulations. Each cohort had its say and the consensus came with a decision to establish an independent, Internal Revenue Service-approved foundation to take the problem of the "new poor" to the people through a conference financed by local money. The conference was fashioned from the grass roots up, with thoughtful input of all parties: consumers (some of whom were poor); providers; state, county and city government officials; business and labor representatives; ethicists; third party payors, and administrators. They met as vested, interested panels, each charged with producing their considered view of problems and solutions of health care for the medically poor of the state. After study and consensus with the panels, they convened in a conference, following regular rules of debate, and produced a health policy statement for Oregon's care of the medically poor. Direct results included a coalition of consumers and providers for inincreased health funding for the "new poor" through Title XIX funds, a call for a conference on bioethical issues, a series of epidemiological studies to accurately define the size of the problem of the "new poor" and increased public awareness of health care delivery problems. The consequent solidarity of purpose was voiced by the immediate past president of the Oregon Medical Association while testifying for the medically poor before the state legislature's Human Resources Committee: "This is the first time I have testified before a legislative committee and not been afraid to turn my back to the audience." A legislator on the committee replied, "Doctor, this is the first time I have been on your side." This is how it should be done for it resulted in a budget-cutting legislature appropriating 10 million dollars for the medically poor.

Conclusions

Physicians are wise to see health planning as a permanent part of health care delivery and, though now in a major transition, it may well emerge as an even more powerful community instrument. In order to focus health planning on prudent service to the sick, physicians must extend their clinical thinking to a new order of complexity which will successfully articulate community medical needs to government, business, labor and citizens in general. The new role demands an ability to understand and talk the "languages" of all those involved in health policy, facilitating full, open discussion that will lead to wisely informed, political consent by the public. The ultimate reward for physicians comes as our professional autonomy is enhanced by a public grateful for recognized service in achieving an enlightened and expanded community consensus.

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Medical Education

Educating Internists in Emergency Medicine

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The education of internists in emergency medicine needs to be thoughtfully planned by those involved in their education. Objectives for their emergency medicine rotation include the recognition and initial treatment of true medical and surgical emergencies, clinical experience with and knowledge of common acute primary care problems, the ability to handle several patients with problems having different degrees of urgency, effective use of consultants in the follow-up and management of difficult patients and a knowledge of and clinical experience with the prehospital care system. A curriculum should be designed to give the resident a core of didactic material in addition to supervised clinical experience. The rotation should be evaluated by both residents and faculty from internal medicine and emergency medicine to determine if it is accomplishing the objectives set forth.

(Sanders AB, Kobernick ME: Educating internists in emergency medicine [Medical Education]. West J Med 1984 Oct; 141:534-537)

Educating internal medicine residents in emergency medicine has typically been confined to clinical experience in hospital emergency departments during one- to three-month rotations. No clearly recognized objectives, curriculum or core body of knowledge and skills has been described. An objective assessment of competence in emergency medicine does not exist as it does in other areas of internal medicine. This state of confusion often leaves residents uncertain about what they should learn from their emergency medicine rotation. Moreover, program directors are often not sure how to evaluate the emergency medicine experience.

Over the past decade emergency medicine has emerged as the 23rd specialty with its own residency training programs, core curriculum and certification examination. Those involved in emergency medicine education have concentrated their efforts on emergency medicine residency training, defining a curriculum and certifying competency for physicians practicing emergency medicine as their specialty.[1-3] Some effort has been made to define objectives and outline a curriculum in emergency medicine for medical students[4]; however, very little attention has been given to residents training in internal medicine, surgery or family practice who spend several months in the emergency department.

The development of emergency medicine as a specialty, the definition of its core knowledge and skills and the creation of training programs with dedicated educators in emergency medicine should all be regarded as positive steps for internists. Much of the knowledge and skills overlaps with that in internal medicine, and the emergency medicine rotation provides an opportunity to develop expertise in a unique clinical setting unmatched by the medical wards, clinics or subspecialty consultation services.

Objectives

The first step in approaching this problem is to design realistic objectives for internists in emergency medicine. What should an internist know about emergency medicine? We propose the following objectives:

- *Recognition and initial treatment of true medical and surgical emergencies.* Internists need to be aware of true emergencies even if they are not the ones who will primarily care for the patients. They also must be capable of initial resuscitation and stabilization efforts. For example, a patient presenting with a clinical picture consistent with a central retinal artery occlusion must be treated immediately even though an ophthalmologist will institute more definitive care. Initial management of a patient with, say, a dissecting aortic aneurysm or intestinal obstruction, clearly lies in the realm of the internists.

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• *Clinical experience with and knowledge of common acute "non-internal medicine" primary care problems.* Many of these acute problems will present in an office or clinic practice and the emergency department exposure is the only opportunity that an internal medicine resident will have to approach these problems. These might include animal and arthropod bites and stings, simple lacerations, corneal abrasions, ankle sprains and the like.

• *The ability to treat several patients with problems of different degrees of acuteness.* While the emphasis in internal medicine training is on thoroughness and comprehensive care, the emphasis in the emergency department is on the presenting problem and its relative urgency. Often residents are asked to manage several patients at once and to make decisions regarding triage priorities.

• *Effective use of consultants in follow-up and management of difficult patients.* Emergency physicians, like internists, will often refer specific problems to outside consultants. Training in what types of cases primary care practitioners can follow and which should be referred, and the urgency of referral, is a skill that must be learned. For example, it is appropriate for a primary care practitioner to follow most cases of ankle sprain after conservative treatment; however, a patient presenting with pain in the "snuffbox" of the wrist after a fall and with no radiographic fracture needs the wrist immobilized and then to be referred to an orthopedist for a possible navicular fracture.

• *Knowledge of and clinical experience with the prehospital care system.* Over the past decade prehospital care has become an important part of our medical care system. Internists should be familiar with the training and function of paramedics and emergency medical technicians (EMT) and of concepts of trauma centers, triage and disaster planning.

Curriculum

The structure of the emergency medicine rotation will vary depending on the service needs of an emergency department and its basic staffing pattern. Nevertheless, certain similarities will exist. The experience should consist of a planned combination of didactic material and clinical experience. The on-line clinical duty in which a resident evaluates and treats patients in the emergency department should consist of 40 to 60 hours per week. Less than 40 hours will give residents too little clinical exposure for the variety of problems with which they must have experience. Clinical time of more than 60 hours per week tends to make a rotation purely a "service" experience and gives residents little time or incentive to study the essential didactic material. The clinical experience must be directly supervised by attending physicians capable of and interested in teaching residents about emergency medicine. The exact mechanism for this supervision will vary from program to program but this mechanism must be clear to the residents, allowing a means of educational feedback regarding the clinical problems they are encountering. The optimal method will be to use full-time emergency medicine faculty to review each patient and be available for immediate consultation. A program of unsupervised residents in an emergency department relying on a resident consultant for their education and assistance with patient care is inadequate to accomplish the goals enumerated above and may lead to poor patient care. Also, dividing an emergency department into subspecialty sections and having medical residents see only medical problems and surgical residents only surgical problems will not accomplish the goals described.

Didactic material should consist of lectures, handout material, pertinent journal articles and book chapters. This material should be given or made available to residents at the beginning of their rotation. It should be of a length that residents can realistically master during their rotation. It must be made clear at the beginning of the rotation that this material is the core of didactic material that they are expected to learn during their emergency medicine rotation. Pursuing one topic in greater depth should, of course, be encouraged depending on the goals and interests of individual residents. Handing a resident a two-volume textbook of emergency medicine and expecting that person to master the knowledge therein in a one-month rotation is impractical.

The exact nature of the core material presented to residents must be determined by the residency directors and the educators in charge of their emergency medicine rotations. Determination of content should be based on departmental priorities, faculty and laboratory resources, the year of postgraduate training and total time spent in the emergency department. In this paper we propose areas of core content that should be considered and given suitable priority when making the decisions regarding an individual rotation.

• *Cardiac life support.* The material presented in the textbook of advanced cardiac life support by the American Heart Association should be a part of the knowledge base of all medical residents. This may be provided as a separate advanced cardiac life support course at the beginning of their residency or in various lectures in their cardiology training. If it is not formally provided elsewhere, the algorithms for managing cardiac arrest and the pharmacology of advanced cardiac life support drugs, together with new developments in controversies in the area of cardiopulmonary resuscitation, should be presented in the form of lectures, handouts or simulated megacode testing stations.

• *Advanced trauma life support.* The Committee on Trauma of the American College of Surgeons has developed an advanced trauma life support course designed to teach primary care physicians advanced lifesaving techniques and stabilization procedures necessary within the first hour of trauma management. Again, this can be given either as a two- to three-day course at the beginning of the residency or if it is not

available as a separate course, the didactic material might be presented in the form of lectures, handouts and so forth, including lectures on priorities in cases of multiple trauma, airway management and shock and thoracic, abdominal, head, cervical spine and extremity trauma. Other elements of this course include an emergency procedures animal laboratory. This laboratory gives residents an opportunity to learn and practice cutdowns, central venous line placement, chest tube placement, peritoneal lavage and cricothyroidotomy. Other practical aspects include the use of the pneumatic antishock garment and cervical spine immobilization.

- *Emergency medical services.* Residents should be given an orientation to the emergency care system in their community. They should be aware of the training and capability of paramedics and EMTs. If possible, an evening spent riding with paramedics would be an excellent experience in prehospital care medicine. The role of communications, hospital cooperation, categorization and designation of specialty centers (trauma centers, burn centers and so forth), disaster planning and triage as part of emergency medical services planning should all be reviewed.

- *Toxicology.* The diagnosis and management of overdoses should be taught with specific emphasis on common drugs and those with antidotes.

- *Environmental injuries.* Material should be presented to residents on the appropriate management of bites and stings (including arthropods, snakes and dogs). Knowledge of other environmental injuries such as hyperthermia, hypothermia, burns, electrical injuries, drowning and trauma should all be reviewed.

- *Common orthopedic injuries.* This material should emphasize treatment of common strains and sprains, dislocations and when a primary care physician can follow a patient or when the case should be referred to a specialist.

- *Obstetric-gynecologic emergencies.* Residents should have knowledge of the workup and management of cases of ectopic pregnancy, pelvic inflammatory disease, acute vaginal bleeding, spontaneous abortion and the dangers of third trimester bleeding.

- *Ophthalmologic emergencies.* Residents should be aware of the clinical presentation and treatment of ophthalmologic emergencies (central retinal artery occlusion, chemical burns) and other problems such as corneal abrasions, conjunctivitis, foreign bodies, iritis and acute glaucoma.

- *Ear, nose and throat disorders.* Residents should feel comfortable managing common ear, nose and throat infections and epistaxis.

- *Neurological problems.* Diseases such as stroke, headaches, central nervous system infections and seizures should be discussed and their management reviewed.

- *Psychiatry.* Residents should be able to deal with suicidal patients, cases of acute psychosis and acute grief reactions and hostile disruptive patients and make an attempt to differentiate organic problems from functional ones.

- *Pediatric emergencies.* Material on child abuse, diarrhea, vomiting, dehydration, meningitis, croup, epiglottiditis, bronchiolitis and asthma should all be presented to residents.

- *Laceration repair.* Handouts, lectures or workshops should be given on suture material, wound infections, wound healing and methods of repairing complicated lacerations.

- *Acute allergic reactions.* Residents should be advised on the management of anaphylaxis and other allergic reactions including asthma.

Evaluation

Both residents and the rotation need to be periodically evaluated as to whether the program is accomplishing the objectives stated. This can be accomplished through objective written pretests and posttests of residents' knowledge of the didactic material and subjective evaluation by both resident and faculty. Evaluation of skills can be accomplished through the use of simulated trauma patients, megacode simulations and records of ability to carry out specific tasks such as chest-tube insertions, central lines or placement of military antishock trousers.

Implementation

An example of one system in which this curriculum has been implemented is the emergency medicine rotation for internal medicine residents at the University of Arizona Health Sciences Center. On the first day of rotation, residents are given an orientation to the Emergency Medical System in Tucson and objectives of the rotation are reviewed. They also go through a dog laboratory in which procedures in emergency medicine are taught, such as venous cutdowns, central venous line placement, diagnostic peritoneal lavage, chest tube insertion and cricothyroidotomy. Then, throughout the month core lectures are given by the faculty covering the basic curriculum in emergency medicine. These monthly lectures include the following topics: Toxicologic Emergencies, Ophthalmologic Emergencies, Pediatric Emergencies, New Developments in Advanced Cardiac Life Support, Chest Trauma, Head and Facial Trauma, Abdominal Trauma, Hand Injuries, Dislocations, Psychiatric Emergencies and Environmental Injuries. These lectures occur near "change of shift" in the morning, so that both the resident getting off duty and the one going on duty may attend. Faculty or senior emergency medicine residents cover clinical duties in the emergency department during these lectures. At orientation the resident also receives a 120-page booklet that reviews and outlines the important points of the 11 core lectures given. It is emphasized that this material is the core knowledge base that we expect the resident to learn during the emergency medi-

cine rotation. Evaluating the rotation is accomplished through subjective evaluation by residents of specific aspects of the rotation and of faculty's teaching ability. Each resident's clinical skills are also subjectively evaluated by all the faculty with whom the resident has worked.

Objective multiple-choice pretests and posttests were given when the system was first implemented. The tests were divided and graded in subsections based on the core lecture material. This gave the instructors a tool to gauge the baseline knowledge of the residents and the effectiveness of their lectures. This is one example of how a core curriculum can be implemented to meet the stated objectives in a one-month rotation. It is practical but requires faculty who are interested in and dedicated to providing a valuable experience in emergency medicine for internal medicine residents.

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A Cost-Benefit Analysis of California's Mandatory Premarital Screening Program for Syphilis

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As do most states, California requires premarital serologic tests for syphilis. The Venereal Disease Research Laboratory (VDRL) test and a fluorescent treponemal antibody-absorbed (FTA-ABS) are often used in series for this purpose. In 1979 in California, there were approximately 300,000 persons tested premaritally, but only 35 were found to have asymptomatic infectious syphilis (incidence = 0.012%). Including all the direct costs of this screening program, the yearly costs of premarital screening is $8.5 million or almost $240,000 per case found. If one takes into account the sensitivities and specificities of the tests, one still has 6 false-negative and 90 false-positive tests using the 1979 figures. The benefits of the program are the number of cases of congenital syphilis that are prevented. Using a worse-case method, no more than 1.5% of the cases of syphilis detected would result in a case of congenital syphilis. The estimated benefits would result in a savings of approximately $161,000. The economic costs of the premarital screening program far outweigh the benefits.

(Haskell RJ: A cost-benefit analysis of California's mandatory premarital screening program for syphilis [Medicine and Government]. West J Med 1984 Oct; 141:538-541)

Since World War II, most states have required couples who are about to be married to be screened for syphilis with a serologic test.[1] This requirement grew out of the tremendous rise in the prevalence of syphilis following the return of servicemen from overseas. However, since that time the yearly incidence of syphilis has declined and some public health officials have questioned the need to continue this expensive screening program.[1-5] Recently, the California state legislature addressed this question, but chose to continue the requirement on the chance that it could prevent "even one case of syphilis." If we know the premarital prevalence of unsuspected syphilis, the sensitivity and specificity of syphilis serologies, the cost of screening and the costs saved in preventing congenital syphilis, then the cost-benefit of routine premarital screening can be determined.

Methods and Results

In California in 1978 there were approximately 300,000 people married.[3] Since most of these were required by law to provide serological evidence that they were not infected with syphilis,[6] it can be assumed that 300,000 Venereal Disease Research Laboratory (VDRL) tests were carried out on this group. The sensitivity (positive test in those with disease) and specificity (negative test in those without disease) of the VDRL test, as a *screening* test in asymptomatic persons, are reported to be 86% and 97%, respectively.[7] Persons who are asymptomatic and have a positive VDRL on a screening examination should undergo further testing to rule out a biologic false-positive test, usually in the form of a fluorescent treponemal antibody-absorption (FTA-ABS) test.[8] This second test has both a sensitivity and specificity of 99%.[7] Given the above information, if one assumes that the characteristics of each test are independent, one can calculate the predictive values for the diagnosis of syphilis using a two-step method (VDRL serology as a screen, followed by an FTA-ABS test in positive cases)[7,9] (Figure1). In 1979 the number of persons identified as having previously undiagnosed infectious syphilis using the premarital screening serologies was only 35.[3] This translates to a very low incidence of approximately 35 per 300,000 per year or 0.012%. One can use this value of 35 as the number of true-positive cases since these are the confirmed cases of syphilis. The sensitivity and specificity of any test is dependent on the population being studied.[7] For example, the VDRL test specificity would be lower if the population consisted of those with chronic or autoimmune disease.[8]

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Because this is a screening test on an asymptomatic population, one would be interested in the positive predictive value of the test (that is, given a positive test, what is the probability that the disease is present). In the case of the asymptomatic premarital population, one could expect only a very poor positive predictive value of 28% when the two serologies are carried out in series (Figure 1).

To determine the *cost* of this screening program, it was necessary to estimate the cost of the serological tests. The cost of the VDRL test ranged from $5.50 at our hospital laboratory to $15 for a commercial laboratory. Since $7 was the charge at one of the largest commercial laboratories in the area,[10] this was used as a representative cost for the VDRL test. The FTA-ABS test was $22 at this same laboratory.[10] Since the law requires an examination, including the serologic test for syphilis,[6] a physician office visit must also be added to the cost of the program. The cost of this office visit is variable depending on the specialty involved, whether it is a first or a follow-up visit and the degree of examination. However, a conservative average cost of $20 per patient was assumed. Using these costs, the direct costs of the program are almost $8.5 million per year (Table 1) or $239,412 per case detected. This does not include the many indirect costs, such as lost wages, the inconvenience of the testing at an already stressful period of time, false-positive follow-ups, false-negatives, adverse reaction to medication and the like.

The major stated benefit of a premarital screening test for syphilis is to prevent newly married couples from passing on their disease to their offspring in the form of congenital syphilis.[1-5] No data are available to determine how many cases of congenital syphilis have been prevented by premarital screening programs. However, assumptions can be made using data in the literature, for an "attack rate" of congenital syphilis in the offspring of those persons found to have infectious syphilis at the time of screening (Figure 2). Using a *very* conservative "worst case scenario," if there were no premarital screening for syphilis, all 35 persons who would have been detected as having presumed infectious syphilis would immediately become pregnant (females) or pass the syphilis to their spouses (males). This would assume that all marriages immediately resulted in pregnancy, no signs or symptoms of syphilis developed and no treatment was given (for syphilis or inadvertently when treating an unrelated disorder). In the first trimester of pregnancy, *Treponema pallidum* cannot cross the placenta and cannot infect the fetus.[11] Because 77% of all pregnant women in the United States in 1979 had prenatal care in their first trimester[9] (that is, 78% of those not receiving care in their first trimester eventually have prenatal care), the risk of congenital syphilis is further reduced when these women are screened and treated (step B, Figure 2). Of the women who receive no prenatal care and remain undetected, there are five possible outcomes of their pregnancy: a normal baby, late abortion, perinatal death secondary to syphilis, an obviously diseased neonate or a child with the onset of defects in later life (later than one year old).[12] Even if these mothers have serologic evidence for syphilis, only 70% of them will infect their offspring[12,13] (step C, Figure 2). This is because almost all women with primary or secondary syphilis will pass the disease to their offspring, but only 80% with early latent and only 30% with late latent syphilis will transmit their disease.[14] Approximately a third of syphilitic mothers will have a spontaneous, late abortion or an induced abortion[14,15] (step D, Figure 2). Of the live births to these others, 25% will be stillborn or die in the perinatal period[14] and 20% will be treated before three months[15] with skin eruptions and rhinitis being the most common manifestations,[14,15] leaving 55% who will remain at risk for late congenital syphilis (step E, Figure 2). This means that in only 0.55 cases out of the original 35 (1.5%) could the major clinical manifestations of late congenital syphilis develop in this conservative approach.[15]

The actual benefits, if this fraction of a case of congenital syphilis could be detected, treated and prevented, are hard to determine because there are no

TABLE 1.—*Direct Costs of Premarital Screening for Syphilis*

Step I	
VDRL in all patients	
300,000 VDRL (@ $7 ea.)	$2,100,000
300,000 Office Visits (@ $20 ea.)	6,000,000
Step II	
FTA-ABS in all positive VDRL patients	
9,034 FTA-ABS (@ $22 ea.)	198,748
9,034 Office Visits (@ $20 ea.)	180,680
TOTAL COSTS	$8,479,428
COST PER CASE DETECTED	$242,269

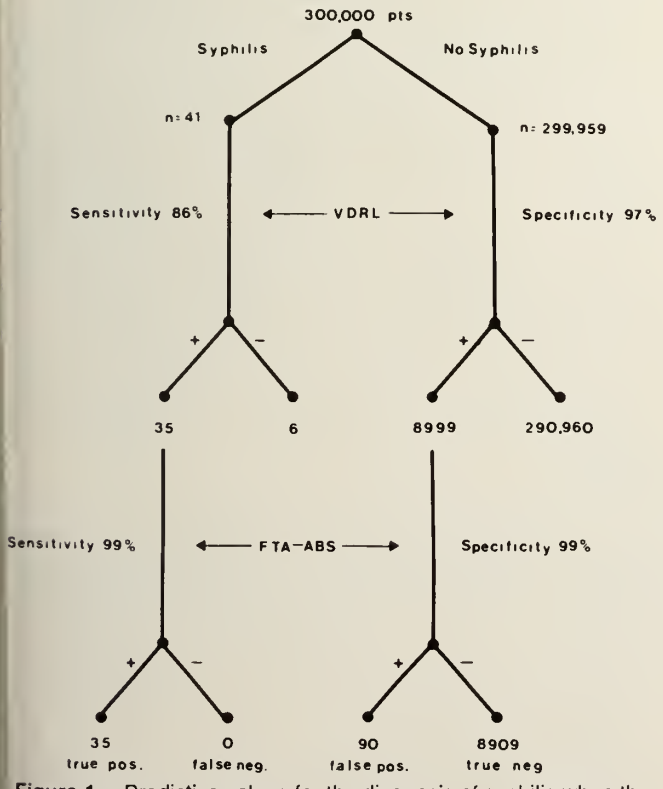

Figure 1.—Predictive values for the diagnosis of syphilis when the Venereal Disease Research Laboratory (VDRL) test is used for screening and, if positive, is followed by the fluorescent treponemal antibody-absorbed (FTA-ABS) test. Patients correctly identified as having syphilis = 35/35 + 90 = 28% = positive predictive value.

estimates of the lifelong cost of each case of congenital syphilis. This would depend on what major defects of the disease manifest themselves—interstitial keratitis, neurosyphilis, Hutchinson's triad, facial-structural abnormalities and the like.[14] The additonal costs to society would be the lifetime cost of medical care and treatment, special education and institutional care. These lifetime costs of care in 1975 for congenital rubella, with its similar problems of blindness, deafness and mental retardation, were estimated as $161,000 per case[16] (approximately $250,000 in today's dollars). Therefore, the economic benefit of a year of premarital screening for syphilis would be approximately $137,500 (0.55 times $250,000), plus the relatively minor costs involved in the small percentage of perinatal deaths, stillbirths and abortions.

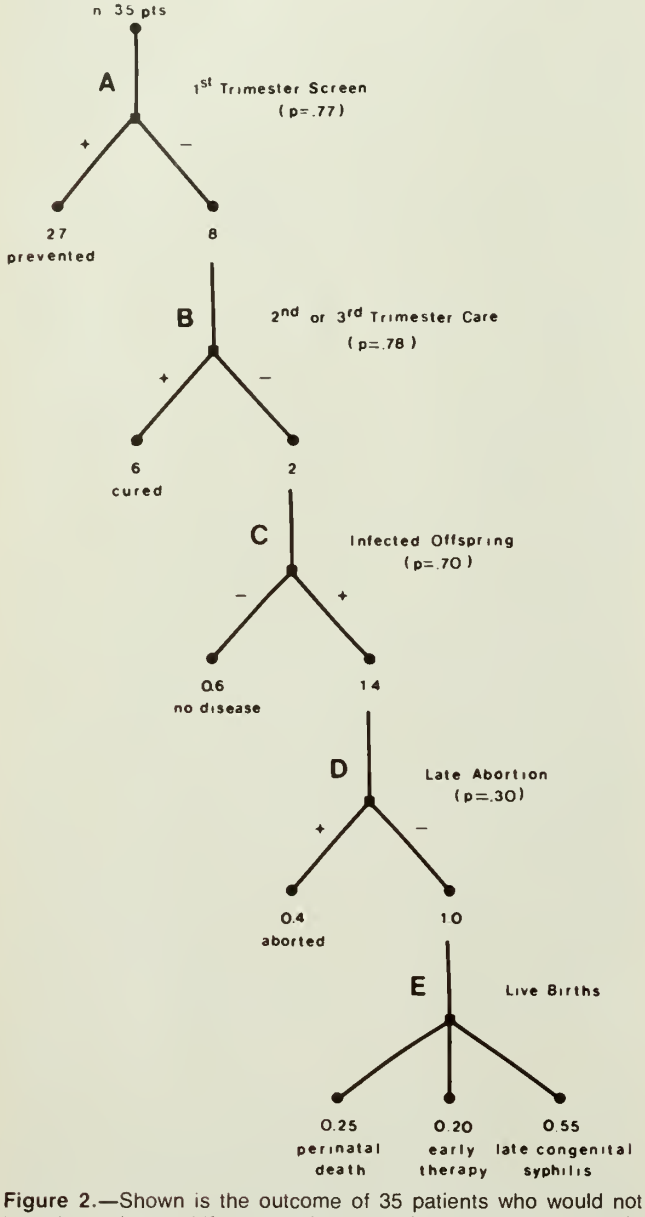

Figure 2.—Shown is the outcome of 35 patients who would not have been detected if a premarital screening program were not in effect. Circles represent results and squares represent decision points. Probabilities of each decision point are in parentheses. Therefore, only 0.55 of 35 cases (1.5%) would result in a live birth with late congenital syphilis.

Discussion

The cost-effectiveness of routine premarital screening for syphilis is a concern of many.[2] Despite the fact that the cost is borne by individual persons and not government, it still represents a cost to society whose efficacy should be proved.

In 1979 only seven states did not require premarital screening for syphilis.[2] California requires that all persons applying for a marriage license have a "standard serologic test, as may be necessary for the discovery of syphilis."[6] Recently, the California state legislature considered, but rejected, the idea of abandoning this mandatory program. Little work has been done on the cost of syphilis screening[2] and none has been done on the benefits of the program.

The results of the cost-benefit analysis presented in this paper suggest that the costs of such a program far outweigh the presumed benefits. Even though there are many assumptions that have to be made in order to estimate the benefits of the program, using a worst-case method defines the most conservative estimate of the benefits. However, even in the extremely unlikely event that all 35 patients who are detected as having asymptomatic syphilis were not detected and each produced an offspring with congenital syphilis who required lifelong institutional care, the estimated lifetime cost would still be only $8.75 million (35 times $250,000), which almost exactly equals the conservative estimate of the cost of the screening program ($8.38 million). However, as was shown, the actual benefits would be far less since only a mere fraction of these persons would actually produce an infected child.

Another argument for abolition of mandatory premarital screening for syphilis is that the time of screening (marriage) and the time of the purported effect of screening (birth of a child) are often very far apart and may be even nonexistent. When the laws for premarital screening were first instituted after World War II, it was more the norm to have a child soon after marriage.[1] However, in today's climate of planned families and career-oriented women, it is not uncommon for couples to delay having children, if any are planned at all, for years after marriage. Between the time of screening and birth of a postponed child, contact with a carrier of syphilis could have occurred with either partner, making the earlier screening useless. Also there is the fact that in many locations as many as a third of births are to unmarried women.[1]

If screening to prevent congenital syphilis is the stated objective of premarital programs, perhaps the money could be best spent screening the target group—pregnant women.[3,4] Most states now require first trimester prenatal screening.[1,2] Perhaps a second serological test before or at the time of delivery would be beneficial since maternal syphilis in the second or third trimester can be as damaging as syphilis existing before pregnancy.[2] Since most cases of congenital syphilis occurred in women who had no serology for syphilis during pregnancy,[12] money could be better spent trying to screen all women before delivery.

This analysis also serves to make another major point: the benefit of any disease screening program is dependent on the prevalence of that disease in the population

studied.[1,7] In a screening test done in an asymptomatic population, the prevalence of disease is likely to be low. Therefore, because in most people tests are likely to be negative, one would want to know, given a positive test, what is the probability that the disease is present (the positive predictive value).[7] The two-step approach to the diagnosis of syphilis, using a VDRL test followed by an FTA-ABS test in all positive cases, has been found to be the most cost-effective screening method for asymptomatic syphilis.[7,17] However, in the group of asymptomatic premarital persons who are screened, the extremely low incidence of 0.012% per year results in a poor predictive value of 28%. Calculation of the positive predictive values for a variety of prior probabilities can help to show when testing for syphilis in asymptomatic persons may be helpful[7] (Figure 3). As ean be seen, as the prevalence of syphilis in a screening population approaches 1%, the positive predictive value begins to exceed 90%. One percent is approximately the prevalenee of asymptomatic syphilis in a random sample of hospital patients[18] and may be even higher in inpatients in lower socioeconomie groups.[19] Using the values developed in this paper (no more than 1.5% of at-risk patients giving birth to a serious case of congenital syphilis), 2,132 people must be found on sereening of the 300,000 premarital examinations to make the eost of screening exactly equal to the cost of benefits. This is an incidence of 0.71% per year and a positive predictive value of about 90%, or an incidence of syphilis that is 50 times the current yearly rate.

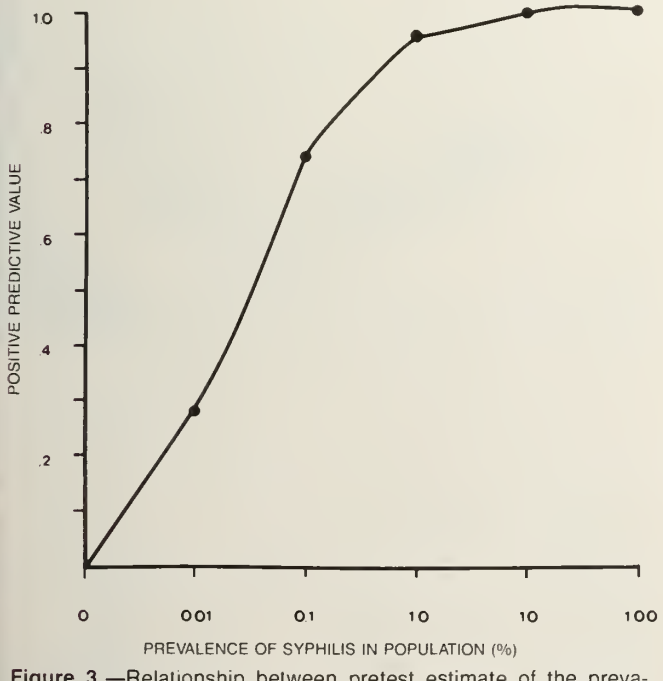

Figure 3.—Relationship between pretest estimate of the prevalence of syphilis in a population and the posttest likelihood of syphilis (positive predictive value).

If the laws requiring a premarital examination for syphilis were repealed, it would be necessary to continue to screen a sample of premarital persons to determine if the yearly incidence of asymptomatic syphilis increases to the point that screening would again become cost-effective.[4,5] It might also be practical to monitor the rate of congenital syphilis in states or cities as they repeal their screening laws to see if there is a significant change in the rate of congenital syphilis among live births. Local epidemiologic data may also indicate a need to screen.[5]

The results of this analysis suggest that routine premarital screening for syphilis has doubtful economie benefit and the costs are high. Unless the incidence of disease changes or the costs of diagnosis or treatment change, it appears that the present program should be abandoned. In its place, a program of screening for syphilis in *all* pregnant women in the first trimester and again at the time of delivery should be established.

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Commentary

The Retired Husband Syndrome

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The retired husband syndrome has become a realistic diagnosis that is found to characterize the symptoms of some of my female patients in the age bracket of 50 to 65 years. In this article I describe the numerous complaints that have been presented to me by women whose husbands have retired.

Retirement

Retirement refers to the discontinuance of a man's normal work habits from 8 AM to 5 PM five days a week and the filling of those hours with pleasurable activities such as fishing, hunting, golfing, gardening or tennis, or engaging in some pleasurable hobby (Figure 1).

During the first years of marriage, each partner tries to please the other by socializing, dining out, going to movies and engaging in recreation of all types, but as a husband becomes successful and takes on more responsibilities at work, he has less time for his wife and loses interest in many of the niceties they formerly enjoyed. She then replaces this lack of attention by seeking out her own recreation, such as bridge, gardening, golfing, tennis or club, volunteer or church work. She becomes dependent on these as a part of her day-to-day living and happiness. As children begin arriving, many of these extracurricular activities are dropped and the former leisure time is replaced with the finalities of raising a family. The husband contributes little because he is busy being successful—sometimes traveling for days and often absent from home from early morning to late evening. When he arrives home, his mood is often one of silence because of his preoccupation with the day's activities, or he often finds time to depreciate or complain of her day's unproductiveness. His demeaning attitude can be tolerated because he is around the home for only short periods of time. But, lo and behold, now he is retired!

As the children came, so they also left. When the rooms are vacated and the couple is again just two, she once more finds spare time to seek out her friends who are also left with fewer responsibilities, and together they take up pleasurable pastimes during their leisure.

With retirement comes a whole new life for both spouses. His is one of finding leisurable activities while hers becomes more involved with details. When a husband retires from his routine workday, his whole attitude toward life turns to doing what he pleases whenever he chooses to do it.

She had never—in 35 or more years of marriage—been aware of the unpleasant personality that suddenly now becomes evident (Figure 2). His normal aggressiveness has now become that of ruling sovereignty; yet, in some cases his dependency takes a major portion of her previously free time. "There is no retirement for me," she exclaims. "In fact, picking up around the house, cleaning the ashtrays and picking up the beer bottles all day make my work load much worse than it was before."

I have frequently heard wives rage with such allegations as, "I am going nuts," "I want to scream," "He is under my feet all the time," "He is driving me crazy," "I'm nervous" or "I can't sleep." These emotional statements are frequently associated with symptoms such as tension headaches, depression, agitation, palpitations, gas, bloating, muscle aches and so forth. Not infrequently a woman will state that previous social functions, such as playing bridge, golfing or meeting with her friends, have had to cease because of his demands for her attention. Even grocery shopping means accompanying her husband and being hit in the heels with a grocery cart.

Then comes the kitchen scene with such complaints as, "Since his retirement, my husband has taken up residence in my kitchen" (Figure 3).

He literally takes over my only domicile and wants to cook or direct the way I cook, and you can't imagine the disarray that can occur. You never saw so many dirty dishes or such unpalatable food in your life. I'm left with cleaning the dishes and trying to salvage a $1.10 dinner out of $21 worth of food, much of which must be discarded. Everything is fried to a charcoal black. His salads are made from every conceivable vegetable and in quantities to fill a washtub. There is enough Roquefort cheese in the salad dressing to strangle an alligator. If he is making breakfast, his hotcakes (which correctly should be called hot rocks) are again served with fried potatoes and eggs. The cracking of eggs is something else. Crushing them with his hands (as presumably he has seen some chef do) always results in picking out egg shell from the food while we attempt to eat it, or throwing the whole damned thing away.

(Johnson CC: The retired husband syndrome [Commentary]. West J Med 1984 Oct; 141:542-545)

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Another harried wife will complain that after breakfast, her husband plants himself in a large chair in the living room, presumably to read the paper, but turns on the television so loud that the walls shake (Figure 4). By the time she finishes cleaning the kitchen, he has settled down in his easy chair, sound asleep, the newspaper scattered all over the floor. She has little time to quickly clean the living room, make the beds and get to her bridge club by 11 AM. No amount of cajoling can get him out of his chair or get his feet off the newspaper. His slippers are lying in the middle of the room. Cigarette butts and the smell of smoke are everywhere. Finally, in disgust, she gives up, dresses and gets ready to leave, when suddenly he wakes up and wants her to go shopping with him. On questioning, he says, "Well, I want to pick out some fishing equipment." As you might know, she (Figure 5) did not go to her club but was escorted from one sports equipment store to another. In a similar vein, another harassed woman came in with a great many physical complaints and, after some discussion, I asked her when her husband had retired. With this, she flew into a rage and began to weep, stating that when she married her husband, she agreed it would be for better or for worse, but never realized it would be for retirement! She went on to elucidate, "He wants me with him every minute (Figure 6). I can't even go to the bathroom without his following. He bought a camper, and I am supposed to go with him every day that he wants to go in that thing—sometimes for several days at a time. After one or two days in this camper, I am mighty tired of picking up his hat to find a place to sit down. To enter the restroom, I must enter sideways, and when inside with the door closed, worry about how in tarnation I will squeeze back out." This closeness is not conducive to a good mental attitude, and she becomes more and more angry because her friends are enjoying a hand of bridge or game of golf, and here she finds herself looking at the closed-in walls of a trailer.

Another aspect that is frequently related by a patient is that the man wants to do all the shopping for food, but on her budget (Figure 7). If she suggests a larger allowance for shopping, he goes into a fit of rage. "I am beside myself," she decries. "I have goosebumps, headaches, dizziness, palpitations and depression."

Another wife protests, "I am so nervous I don't know what to do. Yesterday I wanted to do some shopping for myself, but he insisted he drive me downtown (Figure 8). After leaving me at the store, he announced he would pick me up after driving around the block once. In that time frame it was impossible to even look at fashion apparel, let alone try on for size, or make a wise selection." Another complains with great agitation and obvious depression and tears that since her husband's retirement, he has become an alcoholic (Figure 9). His verbal abuse, total lease on her time and demand for daily sex have produced depression, headaches, rectalgia and total denouncement of sex. Rather than being a pillar in the church, she views herself as only a rug to be thrown about. Until his retirement, she had never been so vividly aware that her husband had an evil or uncontrollable

Figure 1.—Retirement for many is filling his day with what he calls *pleasurable* activity.

Figure 2.—She had never been aware of the unpleasant personality that has suddenly become evident.

Figure 3.—"Since his retirement, my husband has taken up residence in my kitchen—you can't imagine the disarray that can occur."

Figure 4.—"My husband plants himself in a chair in the living room and, after leaving papers and books strewn about, he goes to sleep in the chair."

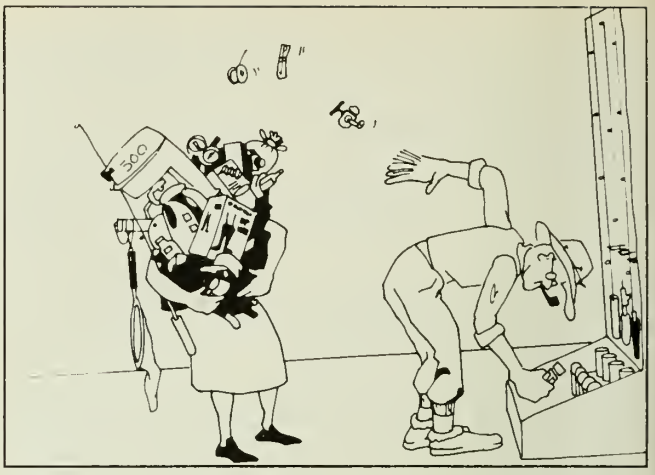

Figure 5.—"He insists I go shopping with him, and the bill for the stuff he bought could have kept us in food, fuel, lights and paid-up taxes for at least two years."

Figure 6.—"He insists I go in the camper with him while he fishes, sometimes for two to three days at a time. After one day, one is mighty tired of picking up his hat to find a place to sit down."

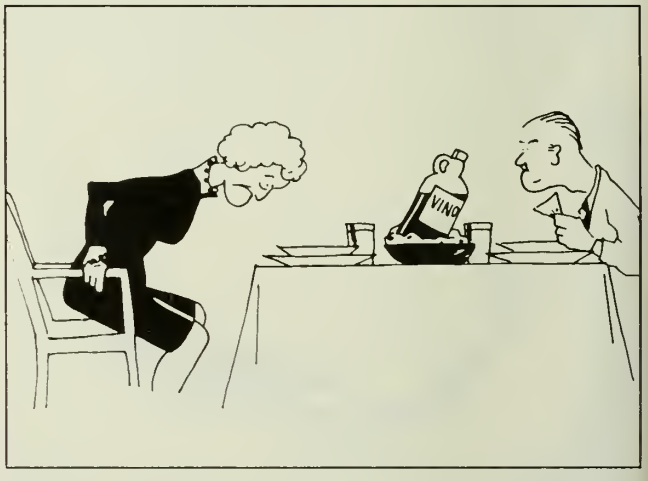

Figure 7.—"Often he wants to do the grocery shopping on my budget, and he brings home cases of beer, Fritos, crackers, potato chips, cigarettes and wine."

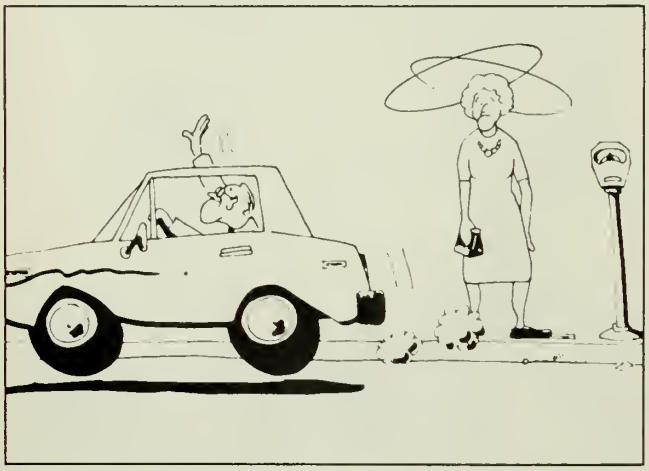

Figure 8.—"After driving me downtown, he left me at the store, said he would drive around the block and then pick me up."

Figure 9.—"He has become an alcoholic, and the verbal abuse I encounter leaves me depressed and ill."

temper and could sulk for hours, and he sees no necessity to make her happy. If she expresses any attempt to get him to do something different from his usual routine, he responds by calling her the world's greatest dummy. Often, he launches into a tirade that may last all evening, one that she has heard at least 100 times previously.

Not infrequently, when a female patient begins to complain of some of the aforementioned symptoms, and she is between 50 and 65 years of age, quite probably she is experiencing symptoms of the "retired husband syndrome." It requires a great deal of sympathy and understanding on the part of a physician and oftentimes involves collaring the husband and convincing him that retirement is not a totally one-sided affair.

It has been said that love cannot be forced but must be earned every day by constant, loving thoughtfulness. There is an old Russian proverb that states, "What you say is drowned out by what you do not do."

Retirement should be a planned program for both spouses with mutual acceptance of both spouses' desires. Also, a productive hobby must usurp a large part of one's day rather than recreation being the major factor in retirement. Happy is the couple who can agree with Browning, who wrote:

> Grow old along with me,
> The best is yet to be;
> The last of life, for which
> the first was made.

Information

A Stepwise Guide for Treating Tuberculosis

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TUBERCULOSIS CONTINUES to be a significant public health problem in the United States. The drugs currently available for the chemotherapy of this disease are sufficiently potent that, when used appropriately, treatment failure and relapse should be an unusual event. Treatment regimens are constantly in a state of evolution and there have been recent major changes in recommended therapeutic protocols. This communication is an attempt to summarize and clarify current recommendations.

Principles Underlying Current Chemotherapy Recommendations

1. Treatment with a single drug fails with high frequency because of antimicrobial resistance.[1]

2. Resistance of *Mycobacterium tuberculosis* to an antimicrobial agent occurs as a result of spontaneous mutation. Such mutation is a chance event.[2]

3. The occurrence of mutation to resistance in a population frequency is about 1 in 10^5 for isoniazid and 1 in 10^6 for streptomycin.[2]

4. Mutational resistance to each drug occurs as an independent event and, thus, the likelihood of a single organism within a virgin population being resistant to two drugs is equal to the product of the independent probabilities. Therefore, the probability of mutation leading to both isoniazid and streptomycin resistance is 1 in 10^{11} (10^5 times 10^6).

5. The number of infective organisms (bacillary load) in a patient varies from 100 or fewer in a person with a positive skin test who has normal findings on a chest radiograph, to about 1,000 in a patient with a small pulmonary nodule, and to as many as 10^5 to 10^{11} in a patient with cavitary disease.[3]

6. In a patient with 10^9 organisms, the chance that a single organism (pretreatment) will be resistant to both streptomycin and isoniazid is 10^9 divided by 10^5 times $10^6 = 0.01$ (1%).

7. The likelihood of the presence of resistant organisms is increased if a patient has been treated previously and if the infection was the result of exposure to a person infected with resistant organisms.[4]

8. Combined chemotherapy with two or more drugs prevents the emergence of strains resistant to an individual drug.

9. Tuberculocidal (as opposed to tuberculostatic) drugs are preferred. These should be capable of killing both rapidly dividing extracellular organisms and, to prevent relapse, intracellular organisms.[5,6]

10. Isoniazid and rifampin are tuberculocidal in both intracellular and extracellular locations. Streptomycin is tuberculocidal extracellularly whereas pyrazinamide is tuberculocidal intracellularly. Ethambutol hydrochloride, para-aminosalicylic acid (PAS) and ethionamide are only tuberculostatic.[5,6]

11. The institution of effective chemotherapy results in a rapid reversal of infectiousness. The risk to household contacts is, for the most part, confined to pretreatment exposure.[7]

12. The major cause of failure of an effective drug regimen is lack of patient compliance.[8]

Management of Uncomplicated Pulmonary Tuberculosis in Adults[9-13]

1. Admission to hospital is generally not necessary.

2. Baseline and follow-up laboratory evaluations should include hematocrit, leukocyte count, platelet count and serum creatinine, aspartate aminotransferase (glutamic-oxaloacetic transaminase) and bilirubin levels.

3. The treatment regimen should start with isoniazid, 300 mg, plus rifampin, 600 mg, by mouth each day as single AM (fasting) doses.

- Warn patients that their urine, tears and saliva will turn orange-red because of the rifampin. Advise them to discontinue the medication and see a physician if a "flu syndrome," bleeding or easy bruising or symptoms of hepatitis occur. About 5% of patients will be unable to complete treatment with this regimen because of toxic reactions, mostly hepatic. However, synergistic hepatic toxicity probably does not occur.
- Be aware of drug interactions. Absorption of isoniazid may be impaired by ingestion of aluminum hydroxide gel. Serum concentrations of phenytoin and carbamazepine are raised by simultaneous isoniazid administration, leading to potential toxicity. Rifampin, because of its ability to induce hepatic microsomal enzymes, can decrease the serum concentration and thus the activity of a variety of drugs, including warfarin, methadone hydrochloride, oral contraceptives, digitoxin, quinidine and corticosteroids.

4. Do a sputum culture monthly until the result is

(Deresinski SC: A stepwise guide for treating tuberculosis [Information]. West J Med 1984 Oct; 141:546-548)

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negative, then culture every two to three months for the duration of treatment regimen. Laboratory examinations (as listed above) may be done as indicated.

5. After two weeks to two months of daily therapy, a physician may elect to either continue daily therapy or to switch to twice-a-week therapy (supervised or unsupervised) with isoniazid, 15 mg per kg (usually 900 mg), plus rifampin, 600 mg. The latter regimen has the potential of increased compliance and decreased cost.

6. Treatment must be continued for at least nine months, including six months of treatment *after* sputum conversion (by culture) is achieved.

7. Posttreatment follow-up is necessary.

- At three, six and 12 months posttreatment, interview for symptoms of tuberculosis, obtain sputum specimen for smear and culture and do chest radiograph *only* if there is a clinical indication.
- After 12 months of follow-up, asymptomatic patients with negative cultures may be discharged with a warning to return if symptoms recur.

Expected Response to Treatment

1. Cough should decrease dramatically within two weeks.[14]

2. If the purified-protein derivative skin test is initially negative, it should become positive within several weeks.[15]

3. Fever, if present, resolves in two thirds of patients within two weeks (median duration, ten days) but may last for months.[16]

4. Conversion of the sputum culture to negative should occur in 93% of patients at 12 weeks and in 99.5% at 20 weeks.[17]

5. The relapse rate of the isoniazid-rifampin regimen is less than 2%, with most of the relapses occurring in the first six posttreatment months.[12]

Retreatment Regimens

1. When relapse occurs after isoniazid-rifampin treatment, the organism almost always remains susceptible to both drugs and further treatment with the same regimen is usually successful.[12]

2. When relapse occurs after regimens not containing both these drugs, the likelihood of resistance is greater and at least two new drugs are required. Stead and Bates recommend the following approach[18]:

- Administer streptomycin, 15 mg per kg, for a maximum of 1 gram; pyrazinamide, 30 mg per kg, and rifampin and isoniazid daily until drug susceptibility test results are available. Then make adjustments as necessary.
- If the organism is susceptible to both isoniazid and rifampin, continue therapy with only these two agents for a total duration of at least nine months.
- If the organism proves to be isoniazid-resistant, continue treatment with rifampin, streptomycin and pyrazinamide for a total duration of at least nine months. If ethambutol is used in place of one of these three drugs, continue administering for at least 12 to 15 months after the sputum culture reverts to negative.

Initial Treatment When Primary Resistance Is Suspected

1. Drug resistance should be suspected when the case is imported from Southeast Asia (25% resistant to isoniazid, 22% to streptomycin, 3% to rifampin, 3% to isoniazid plus rifampin or ethambutol),[19] Mexico[20] or if the case is the result of contact with a patient with a resistant organism.

2. Among the regimens possible, the following two are widely used:

- Start daily treatment with isoniazid, rifampin and ethambutol (15 mg per kg a day). If susceptibility tests indicate that the organisms are susceptible to both isoniazid and rifampin, discontinue giving ethambutol and treat for a minimum of nine months. If resistance is found, alter the regimen and duration accordingly.[9,10]
- Alternatively, treat with isoniazid, rifampin, streptomycin and pyrazinamide as outlined above under "Retreatment Regimens."[13]

Childhood Tuberculosis

1. The federal Public Health Service recommends administering isoniazid, 10 mg per kg, plus rifampin, 10 mg per kg (for a maximum of 600 mg) daily. Hepatotoxic effects occur in about 3% of patients.

2. If a third drug is needed—that is, when there is a suggestion of drug resistance—use ethambutol if visual acuity can be monitored, PAS, 200 to 300 mg per kg a day with a maximum daily dose of 12 grams, or streptomycin, 20 mg per kg a day with a maximum daily dose of one gram.[9-11]

Pregnancy[20-23]

1. A patient with tuberculosis should avoid pregnancy during treatment for her disease. Thus a woman of childbearing age with tuberculosis should be offered contraception. It should be kept in mind, however, that rifampin may decrease the efficacy of oral contraceptives.

2. Streptomycin is ototoxic to a fetus whereas isoniazid and ethambutol appear to be safe. Ethionamide is probably teratogenic. The safety of rifampin is uncertain.

3. A reasonable approach is to use isoniazid and ethambutol for 18 to 24 months. If a third drug is necessary, rifampin may be used.

4. Isoniazid, rifampin and streptomycin—and probably other drugs—are secreted in breast milk.

End-Stage Renal Disease[20,24-27]

Isoniazid and rifampin are metabolized by the liver but their metabolites are renally excreted. Ethambutol is 85% and streptomycin is 100% excreted by the kid-

neys. Isoniazid, streptomycin and ethambutol are removed to varying extents by hemodialysis.

The doses of isoniazid and rifampin are unchanged in the presence of renal insufficiency, with or without hemodialysis. If it is possible, however, isoniazid doses may be adjusted so that the serum concentration is less than 1.0 μg per ml 24 hours after a dose without intervening dialysis. While the appropriate doses of ethambutol and pyrazinamide are not well worked out, administration of 5 mg per kg a day of the former and 12 to 20 mg per kg a day of the latter has been recommended. Streptomycin should be given in a dose of 3 to 5 mg per kg after each dialysis. Monitoring of blood concentrations is desirable.

Severe Liver Disease

It is probably best to avoid the simultaneous use of two potentially hepatotoxic drugs. With severe hepatic dysfunction, doses of isoniazid and rifampin may need to be reduced but no clear guidelines are available.[28]

Patients Who Are Likely to Abscond

1. A treatment regimen with isoniazid, rifampin, pyrazinamide and streptomycin daily for eight weeks, followed by giving isoniazid and rifampin daily for an additional nine weeks results in a relapse rate of 11%.[29]

2. If isoniazid and rifampin therapy is continued for an additional eight weeks (total duration of 25 weeks), the relapse rate is reduced to 1.3%, with most relapses occurring in the first six months posttreatment with organisms that remain susceptible.

3. Alternatively, the use of a twice-a-week regimen with the assistance of local health department personnel may improve compliance.

Extrapulmonary Tuberculosis

The principles of treatment are, in general, the same as for pulmonary tuberculosis. However, if the infection is immediately life-threatening, such as meningitis, acute dissemination or infection in an immunocompromised host, more than two drugs should be used in the initial therapy because of the possibility of drug resistance. Until further information is available, the treatment regimen should probably be continued for about 18 months.[10]

Adjunctive Therapies

Pyridoxine. Patients receiving isoniazid should be given 10 mg of pyridoxine hydrochloride daily if they fall into one of the following groups: pregnant women; patients with a nutritional deficiency (including those with alcoholism and the aged), seizure disorders, uremia or diabetes mellitus, and, possibly, women receiving oral contraceptives.[30]

Adrenal corticosteroids. The use of corticosteroids has been suggested in patients with tuberculous pericarditis, peritonitis and meningitis and for the management of "toxicity." Efficacy, however, except as replacement therapy for adrenal insufficiency, is unproved.

Surgery. The role of a surgical procedure in the management of tuberculosis is quite circumscribed. Pericardiectomy is often required in cases of pericarditis. A nonfunctioning tuberculous kidney may require removal because of complications such as draining sinuses. Cerebrospinal fluid shunting may be necessary to manage obstruction to flow in meningitis.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

PEDIATRICS—Edited by Harold M. Maurer, MD, Professor and Chairman, Department of Pediatrics, Children's Medical Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 1,038 pages, $32.50.

This is the first edition of a new textbook of pediatrics, written almost exclusively by authors from the Medical College of Virginia. In his preface, the editor highlights the difficulty that medical students have with current textbooks of pediatrics in "distinguishing fundamental subject matter . . . from more specialized information . . ." in their study of pediatrics. This text is proposed as an alternative to both the encyclopedic pediatric textbook and the shorter handbooks or manuals. As the book is identified as not being a reference text or a replacement for more comprehensive textbooks, it seems that its real purpose is as an alternative to the shorter texts often used by students who wish to obtain a basic overview of the field. The major points of this review will be an evaluation of its content and the degree to which it succeeds in providing an alternative to texts already available.

The 49 contributors have produced a book containing 34 chapters and a section on laboratory values with age-adjusted norms. There are sections on the major subspecialty areas of pediatrics, pediatric surgery and the surgical specialties, radiology, drug therapy, primary care and the social and emotional problems of children. Each chapter is concluded by a reference section, usually consisting of reference books, review compendia, and occasional journal articles. Most chapters include black-and-white photographs, diagrams, graphs and charts to supplement the text. Organization of the subject matter in individual chapters has clearly been left to the authors and the result is uneven. Some authors have written an introduction to the material and followed it with a clearly outlined approach to specialties in pediatrics, whereas others present material in a scattered fashion which will be of little use to beginning students of pediatrics. Unfortunately, it is this uneven quality that causes this effort to fall short of its mark.

Those chapters that are well constructed will clearly be valuable to students and others who need a basic overview of a topic. For example, the section on immunologic disorders clearly defines the role of the immune system in disease prevention, reviews basic immunologic pathophysiology, outlines the major immune deficiency states by clinical and laboratory measurements and presents material on differential diagnosis, treatment and prognosis. Other chapters, including ones on the cardiovascular and hematologic systems, neoplastic diseases, newborn infants, immunizations, development, genetics, major organ system failure and prevention and care of injury, similarly present material in a way that will be of value to readers with a wide range of training and experience.

The remaining chapters, although containing useful information, suffer from poor organization or spotty treatment of significant topics in pediatrics. For example, the otherwise well-written section on infectious disease begins abruptly with a section on *Hemophilus influenzae* infection. While this is clearly a major area of importance in pediatric infectious disease, the beginning student would be better served by an introduction which highlights the important position that infectious problems occupy in the health care of children. Many other sections would benefit from an approach that considers the perspective of the reader who is likely to use the book.

Finally, there are some statements with which many would disagree. In the chapter on ear, nose and throat, the use of ampicillin is recommended for treatment of epiglottitis, with no mention or consideration of resistant *H influenzae*. The chapter on skin disease identifies *Staphylococcus aureus* as "the most likely primary pathogen" in impetigo. Additionally, there are significant omissions of important topics in pediatrics. The sudden infant death syndrome merits but one mention, with no discussion, and the subjects of apnea, abnormal control of respiration and home monitoring are completely omitted. While the book does not claim to be a comprehensive text, these are major topics in child health care to which students should be exposed.

In summary, this is a first edition whose purpose is to provide students with a core of basic information or to serve as a suitable review text for the practitioner who cares for children. Some chapters do an excellent job of providing a well-outlined framework in a clear, concise manner. The majority, however, suffer from either a lack of focus or an incomplete treatment of their subject matter. Currently, there exist textbooks that are comparable in size to this but are more uniform in presenting a "nonencyclopedic" overview of pediatrics. The key to improving this book in subsequent editions would be to use those successful chapters as a model for the rest in terms of defining objectives, outlining the subject and reviewing major disease entities.

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SEXUAL PRACTICES, THE STORY OF HUMAN SEXUALITY—Edgar Gregerson, Professor, Department of Anthropology, Queens College, City University of New York. Franklin Watts, Inc., 730 Fifth Ave., New York, NY 10019, 1983. $18.95.

If we can accept Gregerson's statement that sex began 2,000,000,000 years ago, then it is high time an anthropological study be done.

That is exactly what Professor Edgar Gregerson has produced. It is a remarkable book, a first, the result of five years of research.

In 1948 Kinsey's Report surprised us with revelations of the intimate sexual habits of the American public. Now, in 1984, Gregerson has compiled a detailed cross-cultural study of the sexual themes, ideologies and customs that have come down to us through the centuries of human progress. It, too, contains surprises.

One does not need to be a student of anthropology to enjoy this book. The reader will be given a new perspective. If we have concerns about sexual permissiveness, women's lib, gay lib or the recent swing toward "unisex," or asexual androgyny, we have only to dip into this unusual book to learn that all this has happened before.

Gregerson writes with a light touch, wittily and with objectivity. This is not "soft-core porn"; the text and the illustrations remind us that sexual artifacts and eroticism have had a pervading influence on sexual themes and societal cultures for all these centuries. Perhaps even for 2 billion years.

E. R. W. FOX, MD
Coeur d'Alene, Idaho

In Memoriam

California Medical Association

CARSON, KATHERINE F., San Diego. Died May 15, 1984, in La Jolla of cancer, aged 61. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1954. Licensed in California in 1955. Dr Carson was a member of the San Diego County Medical Society.

COLE, J.P., La Jolla. Died March 15, 1984, aged 66. Graduate of Columbia University College of Physicians and Surgeons, New York, 1944. Licensed in California in 1954. Dr Cole was a member of the San Diego County Medical Society.

DECKER, RUSSELL M., Pasadena. Died March 1, 1984, aged 79. Graduate of the University of Indiana School of Medicine, Bloomington-Indianapolis, 1930. Licensed in California in 1933. Dr Decker was an associate member of the Los Angeles County Medical Association.

GARRON, LEVON K., Oakland. Died May 5, 1984, in Kanab, Utah, aged 75. Graduate of McGill University Faculty of Medicine, Montreal, 1936. Licensed in California in 1937. Dr Garron was a retired member of the Alameda-Contra Costa Medical Association.

HAMAN, JOHN O., Walnut Creek. Died April 17, 1984, in Walnut Creek, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Dr Haman was a retired member of the San Francisco Medical Society.

LIEBERMAN, BENJAMIN, Oakland. Died May 1, 1984, aged 81. Graduate of the University of Illinois College of Medicine, Chicago, 1927. Licensed in California in 1945. Dr Lieberman was a retired member of the Alameda-Contra Costa Medical Association.

MERCHANT, ALBERT K., Stockton. Died May 19, 1984, in Monterey, aged 83. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Dr Merchant was a retired member of the San Joaquin County Medical Society.

REITZEL, RAYMOND J., San Mateo. Died May 7, 1984, in Burlingame, aged 95. Graduate of Harvard Medical School, Boston, 1924. Licensed in California in 1928. Dr Reitzel was a retired member of the San Mateo County Medical Society.

STEINMETZ, ARTHUR F., Hayward. Died April 15, 1984, aged 80. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1929. Licensed in California in 1931. Dr Steinmetz was a retired member of the Alameda-Contra Costa Medical Association.

Washington State Medical Association

BAILEY, GAYTON S., Seattle. Died February 28, 1984, aged 75. Graduate of Harvard Medical School, Boston, 1934. Licensed in Washington in 1937. Dr Bailey was a retired member of the King County Medical Society.

CHRISTOFFERSEN, OLAF, Seattle. Died July 11, 1984, in Seattle, aged 92. Graduate of Rush Medical College, Chicago, 1917. Licensed in Washington in 1919. Dr Christoffersen was a retired member of the King County Medical Society.

HAGEN, ROBERT F., Lake Stevens. Died April 23, 1984, in Everett, aged 64. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1944. Licensed in Washington in 1946. Dr Hagen was a retired member of the Snohomish County Medical Society.

HOLT, HOWARD P., Yakima. Died May 14, 1984, in Yakima of myocardial infarction, aged 70. Graduate of the University of Arkansas School of Medicine, Little Rock, 1939. Licensed in Washington in 1948. Dr Holt was a retired member of the Yakima County Medical Society.

KNIGHT, D. THERON, Spokane. Died April 11, 1984, in Spokane, aged 63. Graduate of Northwestern University Medical School, Chicago, 1949. Licensed in Washington in 1958. Dr Knight was a member of the Spokane County Medical Society.

LUFT, PAUL H., Spokane. Died June 30, 1984 of injuries received in automobile accident, aged 74. Graduate of Northwestern University Medical School, Chicago, 1942. Licensed in Washington in 1943. Dr Luft was a retired member of the Spokane County Medical Society.

MCILVANIE, SAMUEL K., Spokane. Died July 3, 1984, in Spokane, aged 69. Graduate of the University of Louisville School of Medicine, 1946. Licensed in Washington in 1947. Dr McIlvanie was a member of the Spokane County Medical Society.

PHILLIPS, JOHN A., Kent. Died in March 1984 in Kent, aged 69. Graduate of Loyola University School of Medicine, Chicago, 1945. Licensed in Washington in 1948. Dr Phillips was a retired member of the King County Medical Society.

REW, WILLARD BURNS, Wellesley, Mass. Died June 2, 1984, in Wellesley, Mass, aged 78. Graduate of Harvard Medical School, Boston, 1932. Licensed in Washington in 1936. Dr Rew was a retired member of the Yakima County Medical Society.

WANAMAKER, FRANK H., Seattle. Died June 23, 1984, in Seattle, aged 85. Graduate of Northwestern University Medical School, Chicago, 1928. Licensed in Washington in 1929. Dr Wanamaker was a retired member of the King County Medical Society.

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Note: For rheumatoid arthritis patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established

1. Caldwell J, Brandon ML, Franz KH, et al: A double-blind comparison of the efficacy and side effect liability of tolmetin and indomethacin. Presented at a symposium, *Tolmetin A New Non-steroidal Anti-inflammatory Agent*. Washington, DC, April 1975, *Excerpta Medica* 1976, pp 44-57. See warnings, precautions, and side effects sections in brief summary of prescribing information on next page.

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SUMMARY OF PRESCRIBING INFORMATION

TOLECTIN® DS (tolmetin sodium)
double-strength capsules—for oral administration

Contraindicated: In patients who have previously exhibited intolerance to it, patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. If TOLECTIN must be given to patients with active peptic ulcer, closely supervise for signs of ulcer perforations or severe gastrointestinal bleeding

Precautions: *General*—Ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.

Renal failure, sometimes acutely associated with nephrotic syndrome has been reported. Closely monitor patients with impaired renal function, they may require lower doses.

TOLECTIN prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when TOLECTIN is administered.

In patients receiving concomitant TOLECTIN-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

TOLECTIN should be used with caution in patients with compromised cardiac function.

The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g., sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.

As with other nonsteroidal anti-inflammatory drugs, anaphylactoid reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships which exist among nonsteroidal anti-inflammatory drugs, anaphylactoid reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds, particularly zomepirac sodium. Patients who have had anaphylactoid reactions on TOLECTIN should be treated with conventional therapy, such as epinephrine, antihistamines, and/or steroids.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with TOLECTIN. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue TOLECTIN.

Usage in Pregnancy—Because TOLECTIN has not been studied in pregnant women, use during pregnancy is not recommended.

Nursing Mothers—Because TOLECTIN may be secreted in human milk, nursing should not be undertaken while a patient is on this drug.

Drug Interactions—There have been rare reports that prothrombin time may increase and bleeding may occur.

Adverse Reactions: *Incidence Greater Than 1%*—The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.

Gastrointestinal: Nausea (11%), dyspepsia*, gastrointestinal distress*, abdominal pain*, diarrhea*, flatulence*, vomiting*, constipation, gastritis, and peptic ulcer.

Body as a Whole: Headache*, asthenia*, chest pain.

Cardiovascular: Elevated blood pressure*, edema*.

Central Nervous System: Dizziness*, drowsiness, depression.

Metabolic/Nutritional: Weight gain*, weight loss*.

Dermatologic: Skin irritation.

Special Senses: Tinnitus, visual disturbance.

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred.

Urogenital: Elevated BUN, urinary tract infection.

*Reactions occurring in 3% to 9% of patients treated with TOLECTIN. Reactions occurring in fewer than 3% of the patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable)—*Gastrointestinal*: Gastrointestinal bleeding with or without evidence of peptic ulcer, glossitis, stomatitis, hepatitis, liver function abnormalities.

Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy.

Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis.

Cardiovascular: Congestive heart failure in patients with marginal cardiac function.

Dermatologic: Urticaria, purpura, erythema multiforme.

Urogenital: Hematuria, proteinuria, dysuria, renal failure.

Incidence Less Than 1% (Causal Relationship Unknown)—*Body as a Whole*: Epistaxis.

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdosage, see full prescribing information.

Also available: TOLECTIN® (tolmetin sodium) tablets 200 mg, 100's—Military 6505-01-038-7460, VA 6505-01-038-7460A. Capsules 400 mg, 100's—VA 6505-01-091-9624A.

8/17/83

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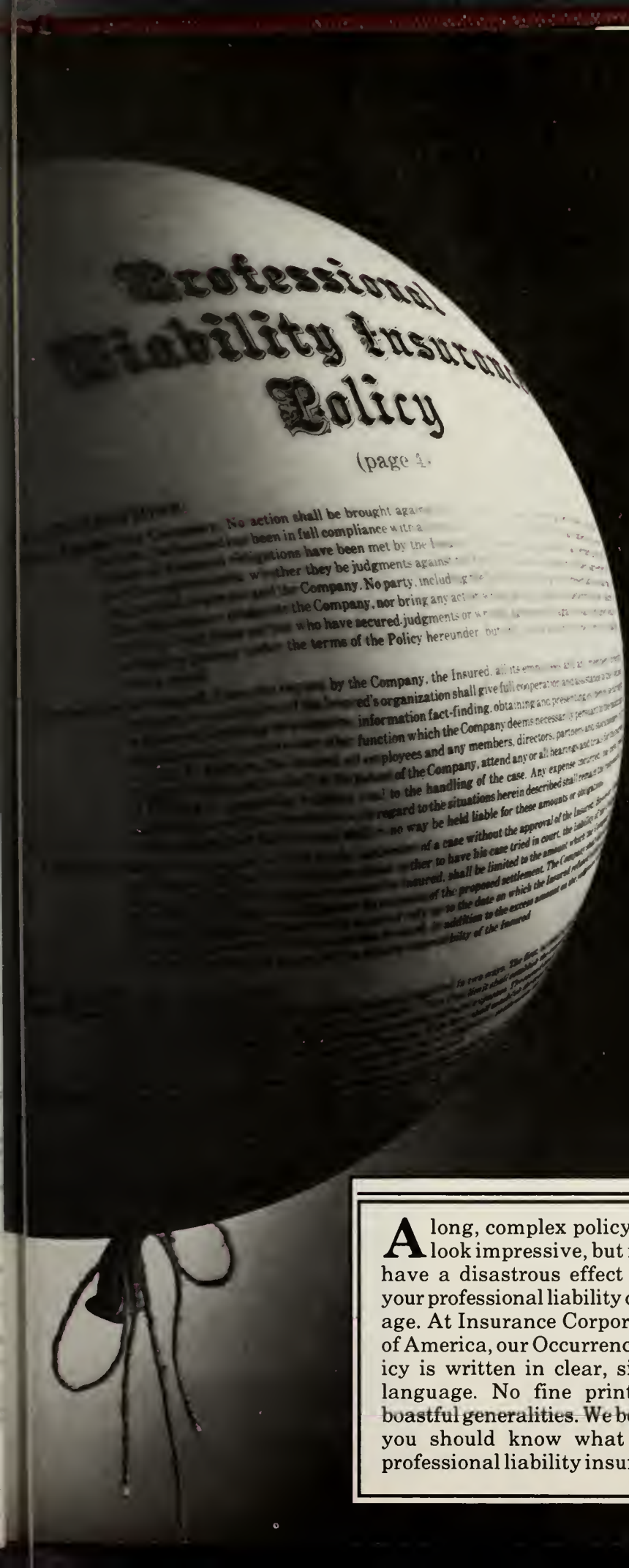

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CONTINUING MEDICAL EDUCATION

(Continued from Page 465)

November 30-December 2—**Fluid and Electrolytes.** Cedars-Sinai Medical Center at La Quinta Hotel, La Quinta. Friday-Sunday. Contact: Lore Kahane, Cedars-Sinai Medical Center, 8700 Beverly Blvd. #2049, Los Angeles 90048. (213) 855-5000.

December 7-8—**Rheumatology for the Clinician.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday.

December 11-13—**7th Annual Midwinter Meeting of the American Endocurietherapy Society** at Wailea Beach Hotel, Maui. Tuesday-Thursday. $250. Contact: AES, 1245 Wilshire Blvd., Ste. 217, Los Angeles 90017.

OBSTETRICS AND GYNECOLOGY

October 22-27—**Review Course in Obstetrics and Gynecology and/or Gynecologic Histopathology.** UCI. Monday-Saturday.

December 13-15—**Gynecologic Surgery.** The American College of OB/GYN at Hyatt Regency Hotel, Los Angeles. Thursday-Saturday. Contact: ACOG, Patience A. Schenck, 600 Maryland Ave., SW, Washington, DC 20024. (202) 638-5577.

OPHTHALMOLOGY

October 20—**Update for Nonophthalmologists: Ocular Diseases of Aging.** JSEI. Saturday.

November 30-December 1—**Phacoemulsification, Extracapsular Cataract Surgery & Intraocular Lenses.** Jules Stein Eye Institute at Los Angeles. Friday-Saturday.

December 7-8—**Glaucoma Management: The State of the Art.** UCSF at Hyatt Regency Hotel, San Francisco. Friday-Saturday.

December 8—**Ophthalmology Association Clinical Meeting.** Jules Stein Eye Institute at Los Angeles. 5 hrs. Saturday. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

PATHOLOGY

November 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday.

PEDIATRICS

October 20-27—**9th Annual Pediatrics for the Practitioner.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: Assistant Director, Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

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For more information, call your local ACS unit or write to the American Cancer Society, 4 West 35th St., New York, NY 10001.

CONTINUING MEDICAL EDUCATION

October 26-27—**Adolescents Inside and Out.** Children's Hospital Medical Center of Northern California and California Chapter 1 of the American Academy of Pediatrics at Doubletree Inn, Monterey, Friday-Saturday. Contact: Gretchen Hayes-Dodd, Medical Staff Office, Children's Hospital Medical Center, 51st and Grove St., Oakland 94609. (415) 428-3334.

November 10—**Physiologic Review of the Fetus and Newborn.** UCSD at Bahia Hotel, San Diego. Thursday-Saturday.

November 16-19—**Clinical Pediatrics.** California Chapters 1, 2 & 3 American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

December 3—**Issues in Perinatal Care.** UCSF. Monday.

December 6-9—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Rancho Mirage. 14 hrs. Thursday-Sunday.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 25-27.

PSYCHIATRY

November 9-11—**30th Annual Group Therapy Symposium.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

RADIOLOGY

October 19-21—**Duplex Scanning.** Institute for Medical Studies at Holiday Inn Fisherman's Wharf, San Francisco. Friday-Sunday. Contact: Kim Stroich, IMS, 30131 Town Center Drive, Ste. 215, Laguna Niguel 92677. (714) 832-2650 or 495-4499.

October 22-26—**9th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Monday-Friday.

November 5-9—**Diagnostic Radiology Seminar.** UCSF at Maui Marriott Hotel, Hawaii. Monday-Friday.

November 14—**Rheumatology—X-ray of the Joints.** LLU. Wednesday.

December 8—**Gastrointestinal Radiology.** Cedars-Sinai Medical Center at Los Angeles. Saturday. Contact: Lore Kahane, PO Box 48750, Room 2049, Los Angeles 90048. (213) 855-5547.

SPORTS MEDICINE

November 9-11—**Sports Medicine and Outpatient Orthopedics for the Primary Care Physician.** Sharp

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Memorial Hospital at Hotel Del Coronado, San Diego. Friday-Sunday. Contact: Jackie Shiller, CMEA. PO Box 84296, San Diego 92138. (619) 223-2997.

SURGERY

October 17-21—**Advanced Microsurgery Training Workshop.** UCSD. Wednesday-Sunday. $1,200.

October 20—**Symposium on Ankylosing Spondylitis and Other Causes of Back Pain.** Cedars-Sinai Medical Center, Los Angeles. Saturday. 6 hrs. $25. Contact: Lore Kahane, Rm 2049, Cedars-Sinai Medical Center, P.O. Box 48750, Los Angeles 90048. (213) 855-5547.

October 21-26—**American College of Surgeons Meeting** at San Francisco. Sunday-Friday. Contact: ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 24—**Spinal Update 1984.** UCSF at Hyatt Regency Hotel, San Francisco. Wednesday. 18 hrs. $295. Contact: UCSF. (415) 666-5731.

October 26-29—**Total Knee and Hip Arthroplasty "Hands On" Course.** Center for Health Education, Long Beach. Friday-Monday. 20 hrs. Contact: Center for Health Education, 2801 Atlantic Ave., PO Box 1428, Long Beach 90801. (213) 595-3811.

October 27—**Lumbar Spine and Pelvis.** UCSD at Hotel del Coronado, Coronado. Saturday.

October 28-November 9—**Temporal Bone Surgical Dissection.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, Dir. of Ed., HEI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 29-November 3—**Basic Microsurgery Training Workshop.** UCSD at Surgery Research Lab, University Hospital, San Diego. Monday-Friday. $1,200.

November 9-10—**American Academy of Facial Plastic & Reconstructive Surgery: Soft Tissue Workshops.** The San Francisco Head and Neck Surgery Foundation at Holiday Inn Union Square, San Francisco. Friday-Saturday. Contact: Cynthia Ashe, SFHNSF, 350 Parnassus Ave., Suite 502, San Francisco 94117. (415) 221-8487.

November 12-16—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday.

November 28-December 2—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday.

November 31-December 2—**Bone Grafting for Maxillofacial Indications.** Plastic Surgery Research Foundation at Hotel Intercontinental, San Diego. Friday-Sunday. $295.

December 1-8—**Temporal Bone Surgical Dissection—1984.** House Ear Institute at Los Angeles. 62 hrs. One week. Contact: Antonio de la Cruz, MD, Director of Education, HEI, 256 South Lake St., Los Angeles 90057. (213) 483-4431

December 3-5—**Current Trends in Total Knee Arthoplasty.** American Academy of Orthopaedic Surgeons at Lake Tahoe. Monday-Wednesday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

December 3-7—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs.

December 6-9—**The Adult Hip.** American Academy of Orthopaedic Surgeons at Rancho Mirage. Thursday-Sunday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

December 12—**Orthopedic Surgery-Arthroscopy—Diagnosis and Treatment.** LLU. Wednesday.

December 14—**A Modern Look at Trauma.** Daniel Freeman Memorial Hospital, Inglewood. Friday. 6 hrs. Contact: DFMH, Dept. of Medical Education. (213) 674-7050, Ext. 3427.

January 9—**Urology—The Prostate.** LLU. Wednesday.

January 14-18—**Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

OF INTEREST TO ALL PHYSICIANS

October 16-18—**Primary Medical Care of Selected Infectious Diseases.** Health Science Seminars of UCSF at Sheraton Hotel, Poipu Beach, Kauai, HI. Tuesday-Thursday. $225. Contact: Cynthia Vaughan, Program Coordinator, PO Box 22023, San Francisco 94122. (415) 861-2713.

October 17—**Second Annual Alcohol & Drug Dependencies Symposium.** Kaiser Permanente Southern California at The Pasadena Hilton, Pasadena. Wednesday. $90. Contact: Judy Harrison—Dept. of Clinical Services, Kaiser-Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

October 18-21—**Clinical Biofeedback Certificate Program.** UCLA. Thursday-Sunday.

October 19-21—**Medical Mycology.** UCSF. Friday-Saturday.

October 22-25—**Primary Care Update: 69th Scientific Assembly of Interstate Postgraduate Medical Association** at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: H. B. Maroney, (608) 257-6781.

October 25-27—**Postgraduate Institute.** CMA at Monterey Sheraton, Monterey. Thursday-Saturday. $150—Non-member, $100—Member. Contact: Janice Rigney (415) 863-5522 Ext. 416.

(Continued on Page 560)

The Physicians' Champion

In 1975... The medical profession was a punching bag. The "malpractice crisis" staggered doctors with successive blows... more and more lawsuits ...bigger judgments... and, soaring insurance premiums.

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New study reveals no interaction between A a

Ativan® (lorazepam) and Darvon® (propoxyphene HCl) ℂⅣ

In a study evaluating the influence of propoxyphene coadministration on the pharmacokinetics of the oxidatively metabolized benzodiazepines Xanax® (alprazolam) ℂⅣ and Valium® (diazepam) ℂⅣ, and a benzodiazepine metabolized by conjugation, Ativan® (lorazepam), the following results were reported:

with Xanax, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance.[1]

in the case of Valium, propoxyphene produced a small but not statistically significant impairment of clearance.[1]

propoxyphene had no apparent effect on the distribution, half-life or clearance of Ativan.[1]

In this randomized crossover study, eight healthy male and female volunteers received single oral doses of alprazolam (1 mg), six received single IV doses of diazepam (10 mg), and five received single IV doses of lorazepam (2 mg), once in a drug-free control state and again during coadministration of propoxyphene (65 mg q6h). Consistent with previous findings, this study evidences that Ativan does not interact with drugs that undergo oxidative metabolism.[2-5] In contrast to most other benzodiazepines, Ativan does not compete for the cytochrome P-450 enzyme system.

The clinical implications of the pharmacokinetic interaction, or non-interaction, of propoxyphene with benzodiazepines are not established by this study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

Caution should also be observed when propoxyphene is prescribed for patients who use alcohol to excess.

References

1. Abernethy DR, Greenblatt DJ, Shader RI: Data on file, Wyeth Laboratories.
2. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology 79:912-916, 1980.
3. Abernethy DR, Greenblatt DJ, Divoll M, et al: Psychopharmacology 80:275-278, 1983.
4. Abernethy DR, Greenblatt DJ, Divoll M, et al: N Engl J Med 306:791-792, 1982.
5. Ochs HR, Greenblatt DJ, Abernethy DR: Data on file, Wyeth Laboratories.

Wyeth Laboratories
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Ativan® for (lorazepam) ℂⅣ Anxiety

See important information on following page.

The appearance of these tablets is a registered trademark of Wyeth Laboratories

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia, some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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Philadelphia, PA 19101

CONTINUING MEDICAL EDUCATION

(Continued from Page 556)

October 26-28—**Weekend Workshop on Stress for Physicians and Spouses.** CMA at Holiday Inn, Napa. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

October 29-November 1—**Interstate Postgraduate Medical Association Meeting** at Las Vegas. Monday-Thursday. Contact: H. B. Maroney, Exec. Dir., PO Box 1109, Madison, WI 53701. (608) 257-6781.

November 9—**New Concepts in Medicine—20th Annual Staff Seminar.** California Hospital Medical Center, Los Angeles. Friday. (213) 748-2411.

November 9-11—**Hawaii Medical Association Annual Meeting** at Kauai Surf Hotel, Kauai. Friday-Sunday. Contact: HMA, 320 Ward Ave., Ste. 200, Honolulu, HI 96814. (808) 536-7702.

November 10—**Infectious Disease.** UCD at Holiday Inn Holidome, Sacramento. Saturday.

November 18—**16th Annual Symposium; "The Newest Concepts in Clinical Practice."** Granada Hills Community Hospital & UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Carol Smith, Granada Hills. (818) 360-1021.

November 30-December 2—**Weekend Workshops on Stress for Women Physicians—Partners Welcome.** CMA at La Playa Hotel, Carmel. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

December 31—**4th Annual Potpourri of Medicine Seminar.** Huntington Memorial Hospital, Pasadena. Monday. 6 hrs. $110. Contact: Med. Staff Coord., Huntington Memorial Hospital, 100 Congress St., Pasadena 91105. (818) 440-5165.

January 23-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** Sir Francis Drake Hotel, San Francisco. Wednesday-Saturday.

January 31-February 2—**Recent Advances in Geriatric Medicine: Dementia in the Elderly.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thursday-Saturday. 13 hrs. $210.

IDAHO

October 18-24—**Effective Diagnosis and Treatment of Infectious Diseases: An EPIC Medical Expedition.** Fishing and Chukar hunting adventure on the Main Salmon River. One week. Sponsors: American Institute of Primary Care Medicine and University of Arizona College of Medicine. 24 hrs. Contact: Richard F. Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

February 20-23—**Big Sky Pulmonary/Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Contact: ALA of Montana, 825 Helena Ave., Helena 59601. (406) 442-6556.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chariman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 26—**Practice Marketing Techniques.** Albuquerque. Friday. Savage Auditorium, Presbyterian Professional Building. Contact: NM Society of Internal Medicine, 303 San Mateo NE, Ste. 204, Albuquerque 97108. (505) 266-7868.

October 27—**Computers in Medical Practice.** Albuquerque. Saturday. Savage Auditorium, Presbyterian Professional Building. Contact: NM Society of Internal Medicine, 303 San Mateo NE, Ste. 204, Albuquerque 87108. (505) 266-7868.

November 2—**Los Alamos Cancer Center Annual Program.** Los Alamos. Friday. Credit hours pending. Contact: Los Alamos Cancer Center, Los Alamos 87544. (505) 662-9620.

November 9-10—**New Mexico Medical Society Interim Meeting—Sports Medicine.** Clovis. Friday-Saturday. 6 hrs. AMA Cat. I. Contact: NMMS, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 15-16—**ABC's of Chronic Lung Disease in Infants, Children and Young Adults.** Albuquerque. Thursday-Friday. 17 hrs. AMA Cat. I. Contact: Winrock Medical Plaza Pediatric Pulmonary Center, 7400 Indian School Rd. NE, Albuquerque 87110. (505) 883-8217.

November 30-December 1—**Trauma Update 84.** Albuquerque. Friday-Saturday. Albuquerque Convention Center/Regent Hotel. 11 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

January 23-27—**New Mexico Metabolism Symposium.** Taos. Wednesday-Sunday. Tennis Ranch. 12 hrs. AMA Cat. I. Contact: Office of CME, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87106. (505) 262-7353.

February 1-3—**Advances in Internal Medicine V.** Albuquerque. Friday-Sunday. 15 hrs. AMA Cat. I. Veterans Administration Medical Center. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

February 21-23—**18th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

March 15-16—**Primary Care Orthopaedics.** Albuquerque. Friday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

April 11-13—**Seventh Annual Pediatric Cardio-Pulmonary Update.** Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phome (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADULT ORTHOPAEDICS—2 Volumes—Edited by Richard L. Cruess, MD, Dean, Faculty of Medicine, and Professor of Surgery, McGill University; Senior Orthopaedic Surgeon, Royal Victoria Hospital, and Chief Surgeon, Shriners Hospital for Crippled Children; and William R. J. Rennie, MD, Associate Professor of Surgery, McGill University; Senior Orthopaedic Surgeon, Royal Victoria Hospital, and Attending Surgeon, Shriners Hospital for Crippled Children, Montreal; with 38 contributors. Churchill Livingstone, 1560 Broadway, New York, NY 10036, 1984. 1,510 pages, $149.00.

ARTERIAL SURGERY—Vol 8 in Clinical Surgery International Series—Edited by John J. Bergan, MD, Magerstadt Professor of Surgery and Chief, Division of Vascular Surgery, Northwestern University, Chicago. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 224 pages, $39.00.

BASIC & CLINICAL PHARMACOLOGY—Second Edition—Edited by Bertram G. Katzung, MD, PhD, Professor of Pharmacology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 888 pages, $26.00.

CHILD NEUROLOGY—A CLINICAL MANUAL—Edited by Bruce O. Berg, MD, Professor of Neurology and Pediatrics and Director of Child Neurology, University of California, San Francisco. Jones Medical Publications, 355 Los Cerros Dr., Greenbrae, CA 94904, 1984. 307 pages, $16.95 (paperback).

CLINICAL PHARMACOLOGY OF SKIN DISEASE—Volume 7 in Monographs in Clinical Pharmacology—David R. Bickers, MD, Professor and Chairman; Paul G. Hazen, MD, Assistant Clinical Professor, and William S. Lynch, MD, Assistant Professor, Department of Dermatology, Case Western Reserve University School of Medicine, Cleveland. Churchill Livingstone, 1560 Broadway, New York, NY 10036, 1984. 312 pages, $39.50.

COLOR ATLAS OF GERIATRIC MEDICINE—Asif Kamal, MBBS, MRCP, Consultant Physician in Geriatric Medicine, St George's Hospital, Lincoln, and J. C. Brocklehurst, MD, MSc, FRCP, Professor of Geriatric Medicine, University of Manchester, England. Medical Economics Books, Oradell, NJ 07649, 1984. 169 pages, $59.95.

COLOR ATLAS OF THE NEWBORN—R. D. G. Milner, MA, MD, PhD, ScD, FRCP, Professor and Head, and S. M. Herber, MB,BCh, MRCP, Clinical Research Fellow, Department of Pediatrics, University of Sheffield, England. Medical Economics Books, Oradell, NJ, 07649, 1984. 131 pages, $44.95.

COMPREHENSIVE APPROACHES TO THE BURNED PERSON—Edited by Norman R. Bernstein, MD, Professor of Psychiatry, University of Illinois, and Consultant, University of Chicago Burn Center, and Martin C. Robson, MD, Professor of Surgery (Plastic and Reconstructive), University of Chicago, and Director, University of Chicago Burn Center. Medical Examination Publishing Co, Inc, 3003 New Hyde Park Rd., New Hyde Park, NY 11040, 1983. 290 pages, no price given (paperback).

DEATH IN THE LOCKER ROOM—STEROIDS & SPORTS—Bob Goldman, Fellow in Sports Medicine, Chicago College of Osteopathic Medicine; Patricia Bush, PhD, Assistant Professor, Georgetown University School of Medicine, Washington, DC, and Ronald Katz, DO, Staff Physician, Chicago College of Osteopathic Medicine. Icarus Press, Inc, PO Box 1225, South Bend, IN 46624. 359 pages, $19.95 (clothbound).

DISASTER MEDICINE—APPLICATION FOR THE IMMEDIATE MANAGEMENT AND TRIAGE OF CIVILIAN AND MILITARY DISASTER VICTIMS—Edited by Frederick M. Burkle, Jr, MD, MPH, Director, Division of Emergency Medical Services, Children's Hospital Medical Center of Akron, and Associate Professor of Pediatrics, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio; Maj. Patricia H. Sanner, MD, Course Director and Faculty, Battlefield Medicine Course, USAF School of Aerospace Medicine, Brooks AFB, Texas, and Col Barry W. Wolcott, MD, Chief of Emergency Medicine, Ft. Lewis, Washington. Medical Examination Publishing Co, Inc, 3003 New Hyde Park Rd, New Hyde Park, NY 11040. 370 pages, no price given (paperback).

FUNDAMENTALS OF NUCLEAR MEDICINE—Edited by Naomi P. Alazraki, MD, Chief, Nuclear Medicine Service, VA Medical Center, and Professor of Radiology, University of Utah Medical School, Salt Lake City, and Fred S. Mishkin, MD, Director of Nuclear Medicine, King/Drew Medical Center, and Professor of Radiology, Drew Postgraduate School of Medicine, Los Angeles. The Society of Nuclear Medicine, Inc, 475 Park Ave South, New York, NY 10016, 1984. 175 pages, price not given (paperback).

HOW TO READ AN ECG—Third Ed—Margaret G. Blowers, RN, BSN, Instructor in intensive coronary care and respiratory nursing care, Nursing Dept, Hackensack Medical Center; and Roberta Smith Sims, RN, MEd, former instructor in intensive coronary care, ECGs and arrhythmias for the Continuing Education Department, Hackensack Medical Center, Hackensack, NJ. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1984. 58 pages, $11.95 plus $1.50 handling charge.

KEY FACTS IN OPHTHALMOLOGY—George W. Weinstein, MD, Professor and Chairman; V.K. Raju, MD, FRCS, FACS, Associate Professor and Assistant Chairman; Larry Schwab, MD, Assistant Professor; Gary T. Raflo, MD, Assistant Professor, and David E. Swanson, MD, Assistant Professor, Department of Ophthalmology, West Virginia University School of Medicine, Morgantown. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 334 pages, $27.00 (paperback).

INTRA-RENAL SURGERY—Edited by J. E. A. Wickham, MS, MB, BSc, FRCS, Director of the Academic Unit, Institute of Urology, University of London; Surgeon, St Peter's Hospitals; Senior Consultant Urologist, St Bartholomew's Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 315 pages, $49.00.

LUPUS: THE BODY AGAINST ITSELF—Updated and Revised Edition—Sheldon Paul Blau, MD, Director, Division of Rheumatic Diseases, Nassau County Medical Center, and Clinical Professor of Medicine, School of Medicine, State University of New York, Stony Brook, New York, and Dodi Schultz. Doubleday & Company, Inc, 245 Park Ave, New York, NY 10167, 1984. 125 pages, $12.95.

CONTINUING MEDICAL EDUCATION

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

(Continued on Page 568)

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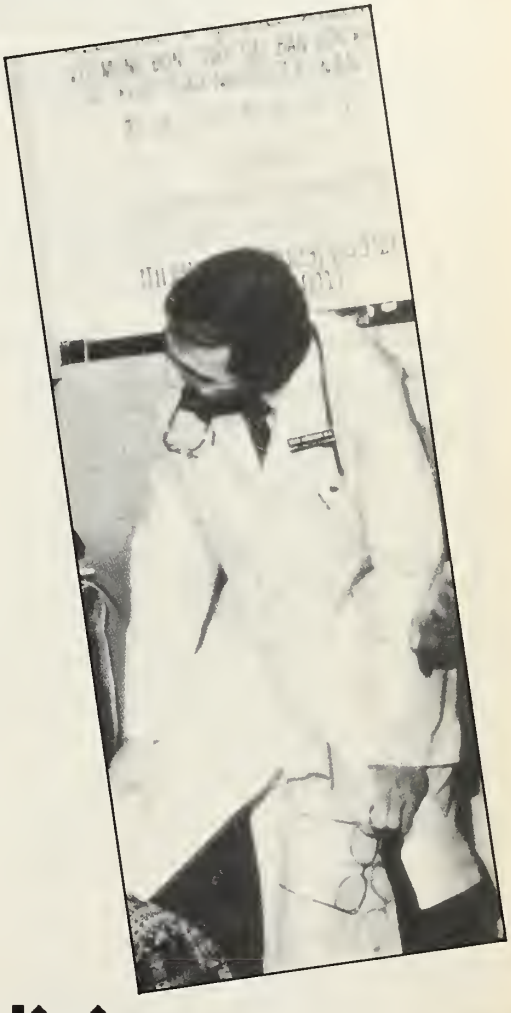

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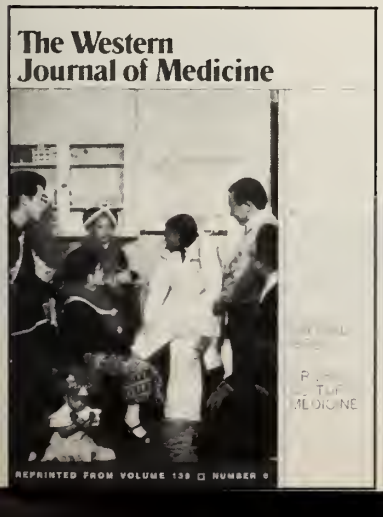

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UROLOGIST, ORTHOPAEDIC SURGEON, OBSTETRICIAN/GYNECOLOGIST AND NEUROLOGIST to join progressive multi-specialty clinic in sunny southeastern New Mexico. Modern facility, family oriented community of 40,000, service area 125,000. Good salary plus incentive bonus paid on production. Many excellent benefits including insurance, paid vacations and continuing education, stock option offered. Immediate openings, call (505) 392-5571, or send CV to Melba Greer, Recruiting Director, Norte Vista Medical Center, Ltd., 2410 North Fowler, Hobbs, NM 88240

OBSTETRICIAN AND GYNECOLOGIST, Southern California—Leading HMO with 28 facilities, 350,000 members and 370 full-time physicians in Los Angeles and Orange Counties has opportunities for OB/GYN specialists. Excellent compensation and benefits. Send curriculum vitae to Director/Physician Recruitment: CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203

CALIFORNIA-URGENT CARE. Positions available for Fall 1984 in free-standing, urgent care settings in several locations. Board certification or eligibility in Emergency Medicine, Family Practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Ave., Suite 500, Oakland, CA 94610, (415) 832-6400

FAMILY PRACTICE OPPORTUNITY. Established Family Practice group located in SW Washington, 15 minutes from Portland. Flexible scheduling. Full partnership available within one year. Contact E. M. McAninch, MD at (206) 834-3141 or send CV to P.O. Box 1004, Camas, WA 98607

DIRECTOR, FAMILY PRACTICE CENTER. Full-time faculty position available in the Department of Family Practice, University of California, Davis; Level of appointment commensurate with academic experience and credentials. Should be Board Certified by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research and academic publication activities. The position will remain open until filled; applications will not be accepted after 12/31/84. Send CV to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd., Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer

LA JOLLA, CALIFORNIA-PULMONOLOGIST needed to join pulmonary-critical care group. Salary and later partnership or early buy-in. Must be BE/BC. Send CV to Box 6444, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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UNIVERSITY OF WYOMING STUDENT HEALTH SERVICE—The Student Health Service has an opening for a full-time physician beginning July 1, 1984. The physician must be Board Certified in Family Practice and have approved resident training or have extensive practice experience. Applicant must be licensed in the State of Wyoming and have at least four years of primary care experience. Physician to join three full-time and three part-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, pharmacy and infirmary. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity-Affirmative Action Employer. Send CV to: Dale C. Brentlinger, MD, Director, Student Health Service, University of Wyoming, University Station Box 3068, Laramie, Wyoming 82071

DIRECTOR OF PREDOCTORAL FAMILY MEDICINE EDUCATION. Full-time faculty position available in the Department of Family Practice, University of California, Davis; level of appointment commensurate with academic experience and credentials. Should be Board Certified by the American Board of Family Practice with interest, training, and/or experience in administration, teaching, research and academic publication activities. The position will remain open until filled, applications will not be accepted after 12/31/84. Send CV to Robert C. Davidson, MD, Department of Family Practice, University of California, Davis, 2221 Stockton Blvd., Sacramento, CA 95817. The University of California is an affirmative action, equal opportunity employer

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NORTHERN CALIFORNIA: Physician, Board certified/qualified in Emergency Medicine or Family Practice, to work part-time or full-time in a busy free standing emergency center. Competitive compensation, malpractice, and bonus for part-time position. Full-time position will also include health insurance, vacation, educational expenses and other benefits. Send CV and references to Joanne Berkowitz, MD, The Emergency Center Medical Group, 4948 San Juan Avenue, Fair Oaks, CA 95628.

FAMILY PRACTITIONER—TULARE COUNTY, CALIFORNIA—Board certified Family Practitioner to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas easily accessed and the Sierra Nevada Mountains nearby. Salary: $75,779-$79,639 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291, (209) 733-6266, An Affirmative Action Employer.

CALIFORNIA, SAN FRANCISCO—Experienced Emergency Department Director wanted for a moderate volume unit. Marketing experience or interest is necessary. Annual salary $60,000+. Send CV to: Emergency Physicians' Medical Group, 1 Maritime Plaza Suite 710, San Francisco, CA 94111.

UNEXPECTED OPPORTUNITY FOR INTERNIST to associate with three busy internists in suburban community 20 minutes east of San Francisco. Reply with CV to Box: 6443, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PULMONOLOGIST, Boarded Int. Med. and Board Eligible Pulmonology, to join 42-member multi-specialty group located on the Central Coast of California. Premium location, excellent practice opportunity with fully paid benefit and retirement program; guaranteed salary first six months followed by incentive pay program; all practice costs paid. For more information contact: Daniel Small, MD, Medical Director or David Graham, Assistant Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401.

OREGON—GENERAL INTERNIST sought for multiple-specialty group. Beautiful rural community, 38 miles from Portland. Send CV to Adm., 420 E. 5th St, McMinnville, OR 97128; phone to staff member (503) 472-6161.

WANTED: University trained general surgeon to join three other general surgeons in 14-physician clinic. Location southern Idaho. Surrounding area abounds in recreational opportunities. Applicant must have excellent qualifications. Send résumé to Box 1233, Twin Falls, ID 83301

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CALIFORNIA—BC/BE Ventura County Group Practice seeks to employ physician to run satellite clinic. Opening scheduled for November, 1984. Please contact Garrett Clifford (805) 482-0773.

(Continued on Page 570)

ARA services

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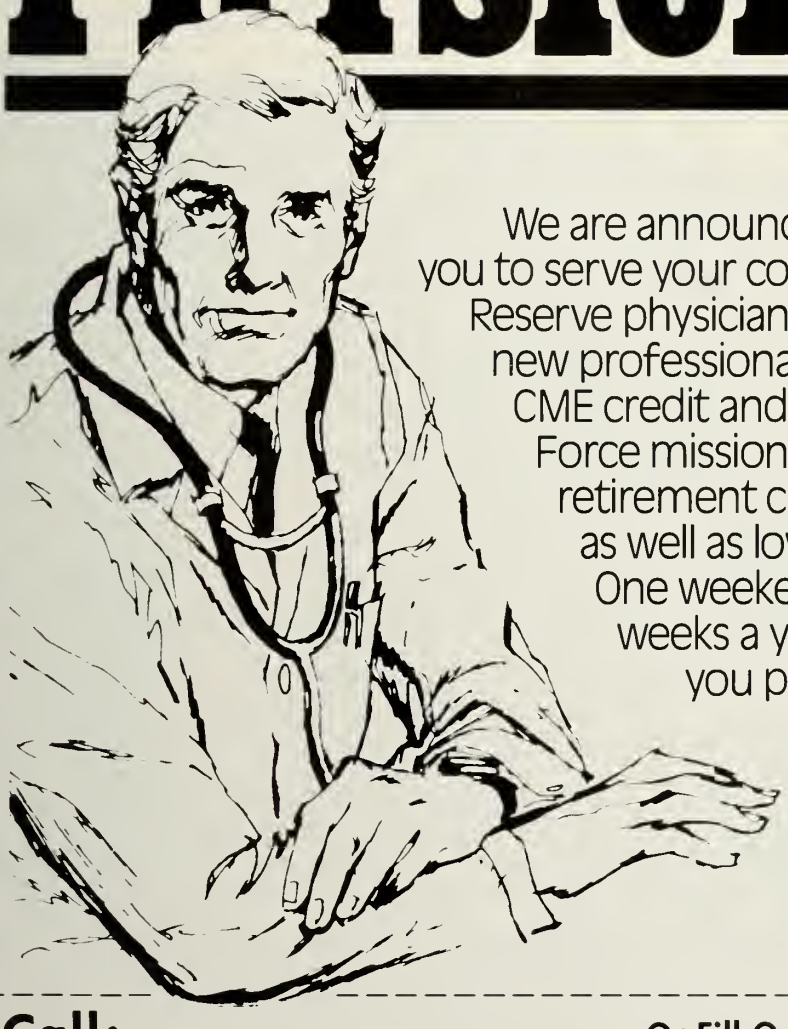

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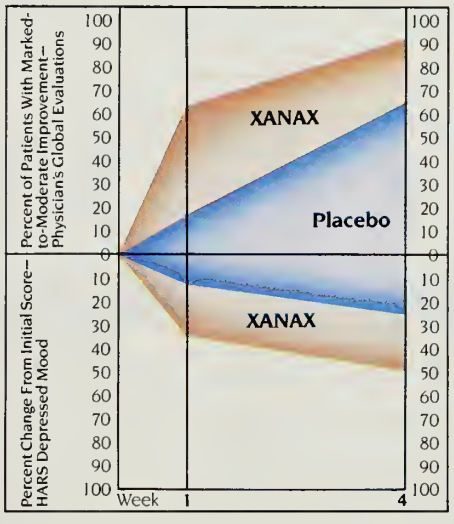
depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).


Percent of Patients With Marked-to-Moderate Improvement—Physician's Global Evaluations
Percent Change From Initial Score—HARS Depressed Mood
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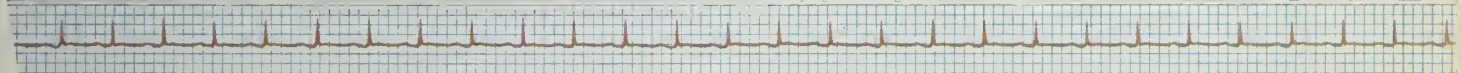

- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file, The Upjohn Company.

Please see next page for brief summary of prescribing information.

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alprazolam C-IV

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions.* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal. Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular Tachycardia/palpitations, and hypotension.

Sensory. Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects. Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

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CONTINUING MEDICAL EDUCATION

(Continued from Page 562)

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

CARDIOLOGY

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OMSU-CME.

EMERGENCY MEDICINE

November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

INTERNAL MEDICINE

December 7-8—**Internal Medicine Update 1984.** Portland. Friday-Saturday. Marriott. Contact: OHSU-CME.

OBSTETRICS AND GYNECOLOGY

October 25-27—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

(Continued on Page 572)

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(Continued from Page 564)

EXCELLENT OPPORTUNITY for Family Practitioners, OB/GYN Physician, General Surgeon, and radiologist in beautiful rugged, eastern Montana Community of 10,000 seeking additional physicians to meet community needs. Excellent school system through junior college. Recreational activities include fishing; excellent pheasant, grouse, water fowl and big game hunting Cross-country skiing locally, downhill skiing only five hours away Modern 46 bed acute and 75 long term care facility offering services in OB, surgery, pathology, lab, x-ray, nuclear medicine, ultrasound, physical and respiratory therapy Guarantee available If interested send CV to John Nordwick, Glendive Community Hospital, Prospect and Ames, Glendive, MT 59330 or call collect (406) 365-3306.

HEALTH OFFICER—Local Health Department serving county-wide population of 390,000. Full-time staff of 143. Comprehensive public health program. Requires California license, MPH and/or Board qualified in Preventive Medicine, three or more years experience in public health administration. Salary $5,489-6,672/month, negotiable. Call or write Jack J. Williams, MD, District Health Officer, San Joaquin Local Health District, PO Box 2009, Stockton, CA 95201. (209) 466-6781; Equal Employment Opportunity Employer.

NEUROLOGIST: Excellent medical and recreational facilities with attractive financial arrangements in association with orthopaedic surgeon for interpretation EMGs and EEGs. Contact: John Paul Jones, Jr., MD, 5116 Hill Road, Lakeport, CA 95453, (707) 263-6435.

IMMEDIATE OPENING FOR SECOND YEAR RESIDENT PHYSICIAN. Contact Medical Director's Office, Community Hospital, 3325 Chanate Road, Santa Rosa, CA 95404; (707) 527-4115.

SAN FRANCISCO BAY AREA: Full-time positions available for physicians board certified or eligible in IM, FP or EM. Unique work opportunity in spectacular freestanding facility located in great community Compensation package includes profit sharing and partnership potential. Send CV to: D. K Templeton, Inc., 7850 Edgewater Drive, Suite 106, Oakland, CA 94610.

ENDOCRINOLOGIST, Board certified or eligible; to join busy Endocrinologist in Bay Area Must have interest in weight control. Write Box 6447, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103.

MEDICAL DIRECTOR (Family Practice or experienced General Practitioner) for growing Primary Care Health Center in South Bay area Supervisory/Management experience required Bilingual (Spanish/English) preferred. Send CV to Gardner Community Health Center, 325 Willow Street, San Jose, CA 95110 EOE M/F/H.

FAMILY PRACTITIONER, BC/BE challenging community clinic work 3 days/plus call, OB included Benefits. CV to Betty Arterberry, Sonoma County Indian Health Project, 2240 Professional Drive, Santa Rosa, CA 95401, (707) 544-4056

NEPHROLOGIST—Board certified or eligible, to join a 150 physician multispecialty prepaid medical group in Hawaii. Stimulating practice; university-affiliated teaching program, excellent fringe benefits Write: Hawaii Permanente Medical Group, Inc., 1697 Ala Moana Blvd., Honolulu, Hawaii 96815 An Equal Opportunity Employer

FAMILY AND COMMUNITY MEDICINE FACULTY—The predoctoral division of the Department of Family and Community Medicine at the University of Arizona is recruiting a full-time physician faculty member for a tenure-track position at the Assistant/Associate Professor level. Board-eligibility or certification in Family Practice or Preventive Medicine desired Applicants must show strong clinical/teaching skills, serious interest in academic Family/Community Medicine and a desire to work closely with medical students. Candidates with practice experience, especially in underserved areas, preferred. Excellent opportunity to join established team developing a problem-based curriculum integrating community and family medicine. Send CV and initial statement of interest to Frank A Hale, PhD, or Ronald Pust, MD, Department of Family and Community Medicine, University of Arizona College of Medicine, Tucson, AZ 85724. Closing date January 1, 1985 or until filled. The University of Arizona is an equal employment opportunity/affirmative action employer.

CALIFORNIA—Modern free-standing walk-in medical center needs physicians. Experience in Family Practice or Emergency Medicine desirable Benefits include flexible work schedules, paid malpractice insurance, profit sharing and more. Respond with CV to: Bernard P. Rudis, MD, 202 W Willow, Visalia, CA 93291, (209) 627-5555

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POSITION AVAILABLE: AAP Board eligible physician for Infant Intensive Care unit. To supplement housestaff physicians' activities and duties. Provide basic "hands on," first-line care of all patients in unit Supervised by Attending Neonatologist. Temporary or permanent beginning January 1, 1985. Two physicians may share the position Average 50 hour/week; mostly evenings and weekends. Hourly rate equivalent to annual salary of $56,000 Liability insurance provided, free access to educational activities. Washington State License required. Write to Dr William Truog, Director, Infant Intensive Care Unit, Children's Orthopedic Hospital, PO C 5371, Seattle, WA 98105.

PHYSICIANS; URGENT CARE—Rapidly expanding medical group servicing Urgent Care Network throughout California (San Diego, Orange County, Bay Areas, San Joaquin Valley, and Sacramento) needs Independent Contractors with Primary Care, ER, Occupational Medicine Specialities. California license required, prior outpatient practice a plus Client provides all personnel facilities, ancillary equipment with Group providing malpractice. Guaranteed minimum plus monthly incentive, stock options available. No relocation assistance. Contact: Personnel, Urgent Care Centers of America, Inc., 2737 Walsh Ave., Santa Clara, CA 95051; (408) 727-1900. EOE.

FAMILY PRACTITIONER/EMERGENCY PHYSICIAN: MD multispecialty group is seeking second MD to staff urgent care clinic. Partnership potential. Board qualified in Family Practice/Emergency Medicine. Beautiful coastal location. Send CV to James Beckett, MD, Santa Cruz Medical Clinic, Santa Cruz, CA 95062.

ORTHOPEDIC SURGEON, Sun Valley, Idaho. Energetic Orthopedic Surgeon to practice with multi-specialty group. Well equipped adjacent hospital. Quality of life high, income moderate. Curriculum vitae and references with first letter please. Dr Lynn T Levy, PO Box 66, Sun Valley, ID 83353.

FELLOWSHIP IN GENERAL INTERNAL MEDICINE—UCSF/San Francisco General Hospital. Two year program emphasizing clinical research, teaching, patient care and management skills. Available July 1985. Applicants must be Board eligible. Contact Richard J Haber, MD, Chief, Division of General Internal Medicine 5H22, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110.

SAN FRANCISCO—Expanding Health Plan has fulltime positions available now for Board certified internists as Primary Care Physicians, and part-time positions for urgent care. Please send CV to: Medical Director, French Hospital Health Plan, 4131 Geary Blvd., San Francisco, CA 94118

PHYSICIANS, full-time, Sacramento unit of Pacific Bell Medical Department Clinical and administrative responsibilities. Highly competitive salary and benefit package. Contact Dr A. S. Maida at (408) 491-2973.

PEDIATRICIAN—Twenty-nine physician multispecialty medical group seeks full-time Board certified/eligible Pediciatrician also interested in some Neonatology to join two others in specialty. Attractive compensation and benefits. Starting date negotiable. Please send CV to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd., Los Angeles, CA 90004; phone (213) 386-8440.

PUGET SOUND AREA, WASHINGTON: Primary care practice located in Lakewood, Washington, a family oriented community of 600,000. No buy-in, regular hours, guaranteed base compensation with incentive, malpractice and other fringes. Beautiful area surrounded by lakes on east and Puget Sound on west. Send CV to Michael Goluska, MD, CHEC Medical Centers, 2200 Sixth Ave., Suite 1200-BB, Seattle, WA 98121 or call collect (206) 624-6888.

PULMONOLOGIST—La Jolla, California, experienced in all aspects of Pulmonary and Critical Care Medicine. Experience in exercise physiology required to establish pulmonary exercise testing and rehabilitation program Must be competent to provide call coverage in cardiology and general internal medicine. Knowledge of bronchoscopy and biopsy techniques, Swan-Ganz Catherization. Must be willing to travel to Imperial County Salary from $65K, depending on experience. Send résumé to Dennis Castillo, MD, 9844 Genesee Ave., La Jolla, CA 92037.

FAMILY PHYSICIAN—Board certified or eligible to join the Family Practice Dept. of a growing primary care based, multispecialty group in Northwest Washington. Close to CME and outdoor recreation. Contact Shane Spray, Administrator, Skagit Valley Medical Center, Mt. Vernon, WA 98273; (206) 428-2524

GENERAL RADIOLOGIST seeks ½-time position in South Bay (S.F.). Experienced in routine diagnostic studies plus industrial injury—acute care cases. Reply to Box 6442, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

LOCUM TENENS NEEDED—FP for busy practice with emphasis on Obstetrics. Needed for 4 months beginning December 1, 1984. Contact Judith Babcock, MD, 7935 216th St. S.W Suite E, Edmonds, WA 98020; (206) 775-0681.

LOCUM TENENS SERVICE

WESTERN PHYSICIANS REGISTRY

. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

OB/GYN Board eligible, California licensed fellowship. Experienced Microsurgery, Infertility, Seminology, Hysteroscopy seeks practice opportunity available now. Call Dr Sheth (312) 842-8071; write 2951 King Dr., Chicago, IL 60616.

POSITION WANTED: Physician in academia seeks a challenging position in California to set up a good teaching and training program in Endocrinology and/or Hypertension. Please reply Box 6445, Western Journal of Medicine, 44 Gough St, San Francisco, CA 94103

PHYSICIAN BOARD CERTIFIED IN GENERAL PRACTICE. I am 45 years old and am interested in purchasing a solo practice in Reno, or joining a partnership in Reno, Nevada Member AMA, Nevada Medical Association, etc. Reply Box 6446, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103

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(Continued on Page 572)

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(Continued from Page 568)

OF INTEREST TO ALL PHYSICIANS

October 19-21—**The Salishan Conference: Cardiology.** Gleneden Beach. Friday-Sunday. Salishan Lodge. Contact: OHSU-CME.

November 30-December 1—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME offce for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

November 30—**Sleep Disorders: A Clinical Approach** (Sponsor: University of Utah/Pulmonary Division, LDS Hospital). Friday. Marriott Hotel, Salt Lake City. Credit and fee to be announced. Contact: DuWayne Schmidt, MD, (801) 321-1100.

February 9-16—**8th Annual Update in Clinical Microbiology/Immunology** (Sponsor: University of Utah). Saturday-Saturday. Park City. Fee to be announced. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

(Continued on Page 574)

MEDICAL PRACTICES - BUYING or SELLING
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NO. CALIFORNIA 1428 Irving St., San Francisco, CA 94122 (415) 661-0700

(Continued from Page 570)

PRACTICES AVAILABLE

CALIFORNIA AND WESTERN STATES. HIGH INCOME practices for sale: Ophthalmology, Orthopedics, Radiology, OB/GYN, Psychiatry, Internal, Family, Pediatric, others. Mary Bradshaw, Professional Practice Opportunities, 21 Altamount Drive, Orinda, CA 94563; (415) 376-0762. Sales, Appraisals, Consulting, Placement, Résumé preparation service.

WENATCHEE, WASHINGTON FAMILY PRACTICE: Physician retiring after 40 years. Fully equipped office and nurse to remain to insure success. Beautiful location summer and winter. Outstanding medical facilities in city. Contact—Dr. R.E. Bolton at (509) 662-8213 or 662-8117.

DERMATOLOGY—Southern California, Practice for sale. Established practice in prestigious county. Gross $193K. Beautiful 1,500 sq. ft. suite. Full price $125K. Professional Practice Sales (714) 832-0230.

FOR SALE—Established General Practice near San Francisco. Please Reply to Box 6448, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

A new low price for Motrin ibuprofen

Motrin is priced lower than Clinoril, Feldene, or Naprosyn.

The price of *Motrin* Tablets to pharmacies has been reduced as much as 35%. Patients taking the average dosage should now pay less for therapy with *Motrin* Tablets than for almost any other nonsteroidal anti-inflammatory drug you prescribe...less, for example, than for Clinoril, Feldene, or Naprosyn.

New low price means major savings.

The dramatic reduction in the price of *Motrin* Tablets means substantial savings from now on for your patients and for patients all across the country for whom *Motrin* Tablets are prescribed. And, of course, all strengths of *Motrin* Tablets continue to be available by prescription only.

Please see the following page for a brief summary of prescribing information.

Motrin® 400 & 600 mg TABLETS
ibuprofen

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Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIDNS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGDT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIDNS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIDNS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CDNTRAINDICATIDNS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription. MED B-7-S

Motrin is a registered trademark of The Upjohn Manufacturing Company

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

J-4790 August, 1984

CONTINUING MEDICAL EDUCATION

(Continued from Page 572)

February 12-15—**14th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 28 hrs. Contact: Linda Twitchell, (801) 581-8633.

February 17-20—**26th Annual Ob/Gyn Update** (Sponsor: University of Utah). Sunday-Wednesday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 20-23—**Reproductive Endocrinology and Infertility** (Sponsor: University of Utah). Wednesday-Saturday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 22-26—**30th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. Fee to be announced. 16 hrs. Contact: Vicky Larsen, (801) 581-6115.

February 25-March 1—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 4-8—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 576)

Chart Your Course

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California physicians:
Arriving at your port soon will be the Annual Session tabloid—the complete program of multidisciplinary scientific courses, CMA House of Delegates activities, special events schedule and advance registration forms.

(Continued from Page 574)

October 15—**What's New in Peds Adolescent Medicine and Surgery.** Walla Walla. Monday. St. Mary's Community Hospital. Contact: U/W.

October 16—**Treatment Alternatives to Breast Cancer.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

October 16—**What's New in Peds Adolescent Medicine and Surgery.** Richland. Tuesday. Cavanagh's Motor Inn. Contact: U/W.

October 17—**What's New in Peds Adolescent Medicine and Surgery.** Yakima. Wednesday. Yakima Memorial Hospital. Contact: U/W.

October 18—**What's New in Peds Adolescent Medicine and Surgery.** Wenatchee. Thursday. Central Washington Hospital. Contact: U/W.

October 19—**Post-Masectomy Breast Reconstruction.** Seattle. Friday. Riverton Hospital. Contact: U/W.

October 19—**Annual Cancer Conference: Early Screening and Detection.** Seattle. Friday. Contact: VMMC.

October 20—**Medical Alumni Day.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

October 25-26—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Museum of History and Industry. Contact: U/W.

October 26—**Evaluation of Bleeding Patients.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 1-2—**Washington Chapter—American College of Emergency Physicians.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, WACEP, 2033 Sixth Ave., #900, Seattle 98121. (206) 623-4801.

November 1-2—**Drug Therapy.** Seattle. Thursday-Friday. HUB-Upper Campus. Contact: U/W.

November 2—**Head and Neck Pain.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 2-3—**Asbestos Related Lung Disease.** Seattle. Friday-Saturday. Contact: Ed Oshiro, Medical Education, Group Health Cooperative, 201 16th Ave E, Seattle 98112. (206) 326-7348.

November 8-9—**Alzheimer's.** Seattle. Thursday-Friday. Westin. Contact: U/W.

November 9—**GI Update.** Seattle. Friday. Contact: VMMC.

November 9—**Rehab Stroke Victim.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 9-10—**Microcomputers in Rehabilitation.** Seattle. Friday-Saturday. U/W Health Sciences. Contact: U/W.

November 14-16—**Hyperthermia in Cancer Therapy.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

November 17-24—(HAWAII) **Medicine and Society in History.** One week. Inter-Continental Maui, Maui. Contact: U/W.

November 20—**Management of Thyroid Diseases.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

November 29-30—**Organ Failure and Organ Transplantation.** Seattle. Thursday-Friday. Mayflower Park Hotel. Contact: U/W.

November 30—**DX and Rx Syphilis.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 1—**Radiology for Attorneys.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

December 6-7—**Aging and Elderly.** Seattle. Thursday-Friday. Westin. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Friday. Contact: VMMC.

December 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 8—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

December 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

December 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 18—**Fever of Unknown Origin.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

December 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 26-January 2—(HAWAII) **Medicine, Magic and Religion.** Maui. Wednesday-Wednesday. Royal Lahaina. Contact: U/W.

January 4—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 11—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 11—**Treatable Hepato-Biliary Disease.** Seattle. Friday. Contact: VMMC.

January 15—**General Topics in Hematology.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 18—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 22—**Surgery Circuit.** Vancouver. Tuesday. Inn Quay. Contact: U/W.

January 23—**Surgery Circuit.** Olympia. Wednesday. Tyee Motor Inn. Contact: U/W.

January 24—**Surgery Circuit.** Bremerton. Thursday. Harrison Memorial Hospital. Contact: U/W.

January 24-26—**Annual President's Meeting—Modern Ophthalmic Technology.** Washington State Academy of Ophthalmology at Seattle. Thursday-Saturday. Westin. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

January 25—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 31-February 1—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin. Contact: U/W.

February 1—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 8—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 16—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

February 16-23—(IDAHO) **Internal Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 19—**Total and Home Parenteral Nutrition.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 22—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

February 23-March 2—(IDAHO) **Office Orthopaedics.** Sun Valley. Saturday- Saturday. Elkhorn Resort. Contact: U/W.

March 2-9—(HAWAII) **Medicine in China.** Kauai. Saturday-Saturday. Royal Waikola. Contact: U/W.

March 2-9—(HAWAII) **Electromyography.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 9-16—(HAWAII) **Imaging for Non-Radiologists.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

March 23—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

March 23-30—(HAWAII) **Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 28-29—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences. Contact: U/W.

March 30-April 6—(HAWAII) **Neurology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 11-12—**DRG.** Seattle. Thursday-Friday. Westin. Contact: U/W.

April 13—**Handicapped Infant.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

April 18-19—**Death Investigation.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

April 26-27—**Sexual Assault.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

May 2-3—**Exercising Women.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 15-17—**Infectious Diseases.** Seattle. Wednesday-Friday. Westin. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

June 15—**Radiology Northwest.** Seattle. Saturday. U/W Health Sciences. Contact: U/W. WJM

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 8-11, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and County, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: 1985—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: November 9-11, 1984, Kauai Surf Hotel, Kauai.

Idaho Medical Association—407 W. Bannock St., PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1985—date and place to be announced.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: 1985—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: November 2-4, 1984, OMA Headquarters, Portland (House of Delegates).

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1985—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: 1985—date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1985—date and place to be announced.

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Improving the outlook... in mixed depression and anxiety

A rational approach, combining

- The standard antidepressant: amitriptyline
- The proven anxiolytic: Librium® (chlordiazepoxide HCl/Roche)Ⓥ

Marked improvement often occurs as early as the first week.

Headache, insomnia or GI upsets associated with mixed depression and anxiety often respond quickly.

Feeling better, patients feel encouraged to stay the course—therefore, fewer dropouts due to side effects: $p < 0.006$ compared to amitriptyline.* Patients should be cautioned about the combined effects of Limbitrol with alcohol and other CNS depressants, and about activities requiring complete mental alertness such as operating machinery or driving a car.

*Feighner JP: *Psychopharmacology* 61:217-225, Mar 22, 1979.

A Roche Medication Education Booklet—
"You, your medical problem and your treatment with Limbitrol."

Valuable adjunct to dual therapy with Limbitrol:

Because an informed patient is more responsive...

This easy-to-read brochure explains the rationale of dual therapy with Limbitrol and encourages patient compliance. To obtain a complimentary supply, please contact your Roche representative.

In moderate depression and anxiety

Limbitrol® Ⓥ

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

LIMBITROL® Tablets Ⓥ
Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female; elevation and lowering of blood sugar levels; and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

ROCHE®
ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

CLEARING: BOTH THE DEPRESSION AND THE ANXIETY...

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Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

Please see summary of product information on reverse side.

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The Western Journal of Medicine

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Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Strong on results.

before Color-enhanced photo of *H. influenzae* seen through a scanning electron microscope.[5]

after *H. influenzae* culture after 24 hours' incubation with Bactrim (trimethoprim and sulfamethoxazole/Roche) at 5× MIC. Note long filaments and distorted shapes of bacteria.

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Simple to take.

In acute exacerbations of chronic bronchitis

- Clears susceptible pathogens from sputum[1-4]
- Reduces cough and sputum volume[1-4]
- Reduces evidence of inflammation[1]

Bactericidal *in vitro* against *H. influenzae* (nontypable strains)

Bactrim shows high activity *in vitro* against most strains of *H. influenzae*—even ampicillin-resistant strains. However, *in vitro* data do not necessarily correlate with clinical results.

In morphologic studies,[5] cultures of *H. influenzae* were exposed to Bactrim at 5× MIC. After just four hours, bacteria began to form filaments, indicating an alteration in the normal pattern of cell division. After 12 hours, virtually all bacteria had formed filaments. When these bacteria were removed and recultured in drug-free nutrient medium, almost all were unable to divide and form colonies—a result interpreted as demonstrating that, at the above concentration, the effect of Bactrim on the *H. influenzae* was bactericidal.

Also effective against susceptible strains of *S. pneumoniae in vitro*

In sputum cultures of *S. pneumoniae,* 91% of strains were susceptible to Bactrim.[6]

In acute exacerbations of chronic bronchitis involving *S. pneumoniae* or *H. influenzae,* sputum cultures taken seven days after a two-week course of therapy showed that Bactrim eradicated these bacteria in 91% (50 of 55) of the patients treated.[5]

Effective—and economical—antimicrobial therapy

In three double-blind studies, Bactrim DS *b.i.d.* was unsurpassed by ampicillin *q.i.d.*[1-3]

And in ten clinical comparisons with tetracycline involving nearly 700 patients, Bactrim proved comparable on major clinical parameters: change in sputum purulence, reduction in sputum volume and microbiological clearance of pathogens.[4]

And equally important: the convenient and economical *b.i.d.* dosage of Bactrim DS is designed to encourage patient compliance.

Bactrim™ DS

(trimethoprim and sulfamethoxazole/Roche)

Consistent success on a *b.i.d.* schedule

Please see references and summary of product information on following page.

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Wormser GP, Keusch GT, Heel RC: *Drugs 24*:459-518, Dec 1982. 3. Ronald AR: *Clin Ther 3*:176-189, 1980. 4. Rubin RH, Swartz MN: *N Engl J Med 303*:426-432, Aug 21, 1980. 5. Cunha BA: *Postgrad Med 70*(6):149-156, Dec 1981. 6. Neu HC: *Infectious Diseases 10*(6):4, 19, Jun 1980. 7. Jones SR: *Ration Drug Ther 13*(11): 1-5, Nov 1979.

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions.* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children. Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment. Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

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Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100, Prescription Paks of 40. *Pediatric Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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Note: For rheumatoid arthritis patients classified as Functional Class IV (incapacitated with little or no self-care), safety and effectiveness have not yet been established.

1. Caldwell J, Brandon ML, Franz KH, et al: A double-blind comparison of the efficacy and side effect liability of tolmetin and indomethacin. Presented at a symposium: *Tolmetin, A New Non-steroidal Anti-inflammatory Agent*. Washington, DC, April 1975. *Excerpta Medica* 1976, pp 44-57. See warnings, precautions, and side effects sections in brief summary of prescribing information on next page.

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SUMMARY OF PRESCRIBING INFORMATION
TOLECTIN® DS (tolmetin sodium) double-strength capsules—for oral administration
Contraindicated: In patients who have previously exhibited intolerance to it, patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria.
Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. If TOLECTIN must be given to patients with active peptic ulcer, closely supervise for signs of ulcer perforations or severe gastrointestinal bleeding.
Precautions: *General*—Ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.
Renal failure, sometimes acutely associated with nephrotic syndrome has been reported. Closely monitor patients with impaired renal function; they may require lower doses.
TOLECTIN prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when TOLECTIN is administered.
In patients receiving concomitant TOLECTIN-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.
TOLECTIN should be used with caution in patients with compromised cardiac function.
The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g., sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.
As with other nonsteroidal anti-inflammatory drugs, anaphylactoid reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships which exist among nonsteroidal anti-inflammatory drugs, anaphylactoid reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds, particularly zomepirac sodium. Patients who have had anaphylactoid reactions on TOLECTIN should be treated with conventional therapy, such as epinephrine, antihistamines, and/or steroids.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with TOLECTIN. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue TOLECTIN.
Usage in Pregnancy—Because TOLECTIN has not been studied in pregnant women, use during pregnancy is not recommended.
Nursing Mothers—Because TOLECTIN may be secreted in human milk, nursing should not be undertaken while a patient is on this drug.
Drug Interactions—There have been rare reports that prothrombin time may increase and bleeding may occur.
Adverse Reactions: *Incidence Greater Than 1%*—The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.
Gastrointestinal: Nausea (11%), dyspepsia* gastrointestinal distress* abdominal pain* diarrhea* flatulence* vomiting* constipation, gastritis, and peptic ulcer.
Body as a Whole: Headache* asthenia* chest pain.
Cardiovascular: Elevated blood pressure,* edema*
Central Nervous System: Dizziness,* drowsiness, depression.
Metabolic/Nutritional: Weight gain,* weight loss*
Dermatologic: Skin irritation.
Special Senses: Tinnitus, visual disturbance.
Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred.
Urogenital: Elevated BUN, urinary tract infection.
*Reactions occurring in 3% to 9% of patients treated with TOLECTIN. Reactions occurring in fewer than 3% of the patients are unmarked.
Incidence Less Than 1% (Causal Relationship Probable)—*Gastrointestinal*: Gastrointestinal bleeding with or without evidence of peptic ulcer, glossitis, stomatitis, hepatitis, liver function abnormalities.
Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy.
Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis.
Cardiovascular: Congestive heart failure in patients with marginal cardiac function.
Dermatologic: Urticaria, purpura, erythema multiforme.
Urogenital: Hematuria, proteinuria, dysuria, renal failure.
Incidence Less Than 1% (Causal Relationship Unknown)—*Body as a Whole*: Epistaxis.
Full directions for use should be read before administering or prescribing.
For information on symptoms and treatment of overdosage, see full prescribing information.
Also available: TOLECTIN® (tolmetin sodium) tablets 200 mg 100's—Military 6505-01-038-7460, VA 6505-01-038-7460A. Capsules 400 mg 100's—VA 6505-01-091-9624A
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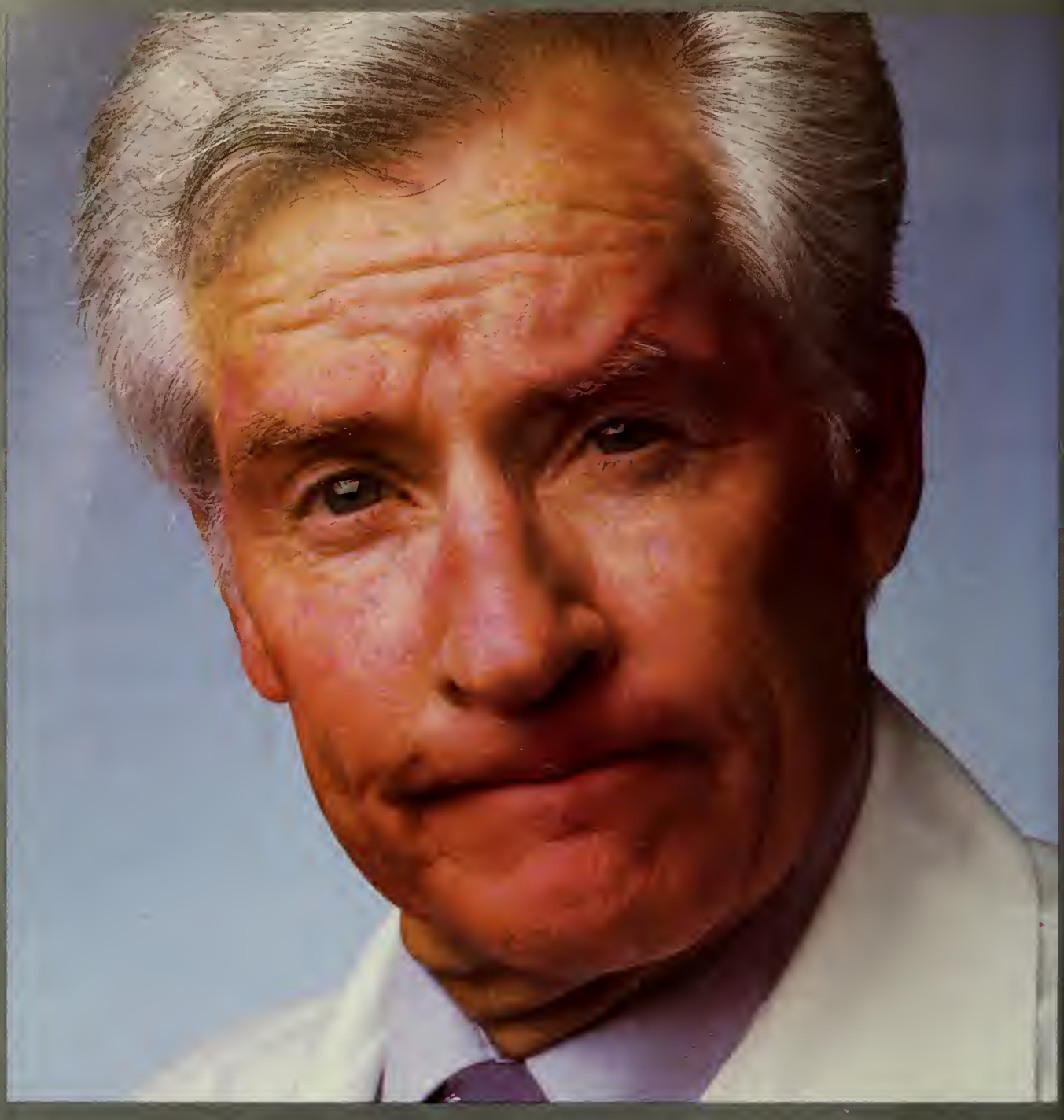

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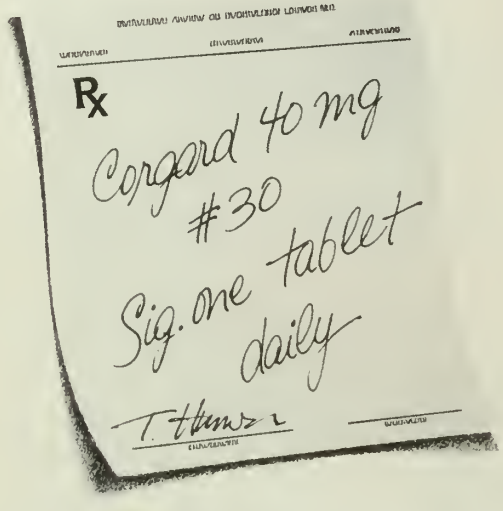

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WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal– Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)– PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery–Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function–Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions–Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy–In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers–It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**– Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis. **Hematologic**–agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

SQUIBB

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Issued: June 1984

The Joint National Committee now advocates beta-blockers for broad Step-1 usage

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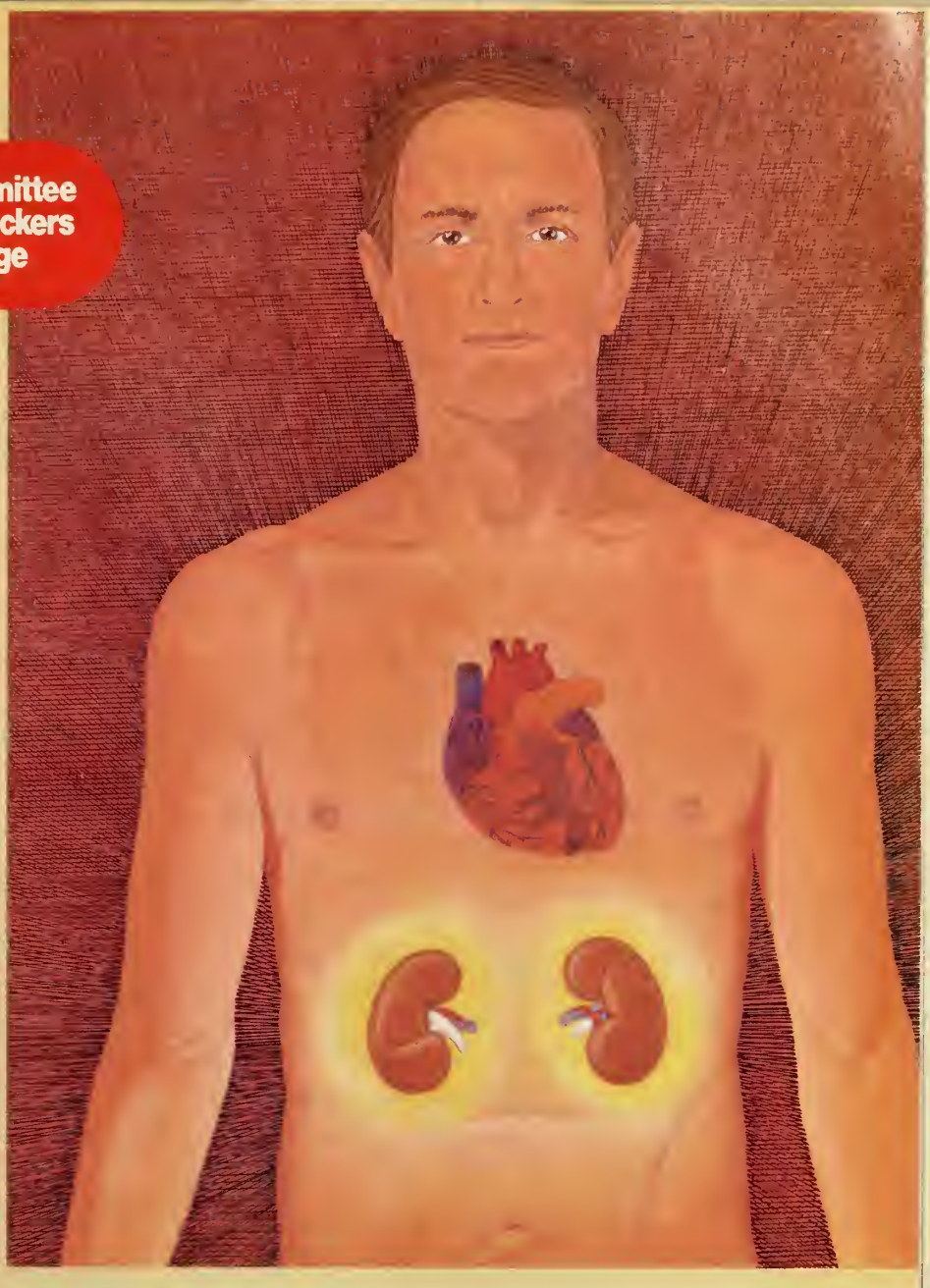
BLOCKS BETA RECEPTORS IN THE HEART WHILE APPARENTLY PRESERVING RENAL BLOOD FLOW



Effect on kidney

"...investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function."[1]

"...the majority of investigators utilizing propranolol have reported decrements in RPF [renal plasma flow] and GFR [glomerular filtration rate]..."[1]

CORGARD® (nadolol tablets) should be used with caution in patients with impaired renal function.

Reference: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Mineral Electrolyte Metab 8: 237-254, 1982.

SQUIBB®
Innovators in cardiovascular medicine

TAKE THE ADVANTAGE TO HEART

Please see the adjacent page of this advertisement for brief summary.

(Continued from Page 585)

EPITOMES OF PROGRESS

Otolaryngology/Head and Neck Surgery

Items of progress in otolaryngology/head and neck surgery. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

672 **Laser Doppler Velocimetry to Predict Skin Flap Survival**
R. E. TRACHY and C. W. CUMMINGS, MD

672 **Emergency Ventilation Using Transtracheal Puncture and Positive Pressure Oxygenation**
ERNEST A. WEYMULLER, Jr, MD

673 **Retrolabyrinthine Vestibular Nerve Section**
DERALD E. BRACKMANN, MD; JOHN T. McELVEEN, Jr, MD; JOHN W. HOUSE, MD, and WILLIAM E. HITSELBERGER, MD

673 **Carotid Artery Grafting in Head and Neck Cancer**
CHARLES F. KOOPMANN, Jr, MD

674 **Otolaryngologic Manifestations of Acquired Immunodeficiency Syndrome**
C. DANIEL SOOY, MD

674 **Auditory Brain-Stem Evoked Response Measurement in Infants**
DONALD MORGAN, PhD, and MARC F. COLMAN, MD

675 **Skin Tests or RAST—Current Concepts**
BERNARD P. CUNNINGHAM, MD

675 **New Approaches to Treatment in Glottic, Subglottic and Tracheal Stenosis**
C. DANIEL SOOY, MD, and H. H. DEDO, MD

676 **Complications of Injectable Collagen**
DALE RICE, MD; FRANK M. KAMER, MD, and MICHAEL M. CHURUKIAN, MD

EDITORIALS

677 **Power on the Demand Side of Health Care**

677 **Sudden Cardiac Death—A Perspective**
ALFRED E. BUXTON, MD, and MARK E. JOSEPHSON, MD

From the Cardiovascular Section, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia.

679 **Physicians' Incomes**

CASE REPORTS

680 **Adult Hemolytic-Uremic Syndrome and Bone Marrow Necrosis**
MAJ CHARLES B. HICKS, MC, USA, and LTC JOHN REDMOND III, MC, USA

From the Internal Medicine Service, Department of Medicine, Letterman Army Medical Center, Presidio of San Francisco, and Department of Medicine, Madigan Army Medical Center, Tacoma, Washington.

682 **Tuberculous Involvement of a Polymicrobial Liver Abscess**
LARRY F. SILVERBERG, MD; CYNTHIA JOHNSTON, MD, and KAI HABER, MD

From the Department of Family and Community Medicine and the Department of Radiology, Arizona Health Sciences Center, University of Arizona, Tucson. Dr Silverberg is now in private practice in Los Angeles.

684 **Severe Intraoperative Anaphylactic Reaction to Dextran 70 Administered Intraperitoneally**
MAURIE MARKMAN, MD; CRAIG E. PFEIFLE, PharmD, and WILLIAM E. LUCAS, MD

From the Departments of Medicine (Division of Hematology/Oncology) and Obstetrics and Gynecology and the UCSD Cancer Center, University of California, San Diego, School of Medicine, San Diego.

CORRESPONDENCE

686 **Pelvic Pain Cured by Pelvic Examination**
HENRY SCHNEIDERMAN, MD

686 **Carcinoma as a Possible Complication of Jejunoileal Bypass Operation**
SALLY VOSS, MD, and THOMAS R. RUSSELL, MD

(Continued on Page 590)

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(Continued from Page 588)

687 **Familial Hiatal Hernia**
ALEXANDER K. C. LEUNG, MBBS, FRCP(C)

687 **Designing New Devices for Measuring Blood Pressure**
JOHN M. GOLDENRING, MD, MPH

687 **Private Sector Financing for Medical Education**
ROLAND C. GRIGGS, MD

688 **Oral Contraceptives and Venous Thrombosis**
CECIL HOUGIE, MD
THOMAS M. KELLY, MD, Replies

689 **Relationship Between Costs and Quality of Medical Care**
KEVIN PATRICK, MD, MS

689 **Enterococcal Endocarditis After Sigmoidoscopy**
JANE L. MURRAY, MD

690 **Methicillin-Resistant *Staphylococcus aureus***
ALAN LIFSON, MD, and BARBARA PAUL, MD

690 **Reye's Syndrome and Salicylates**
ELLIOT M. SACKS, MD

COMMENTARY

691 **The Disuse Syndrome**
WALTER M. BORTZ II, MD

From the Health Care Division, Palo Alto Medical Foundation, Palo Alto, California.

PUBLIC HEALTH AND PREVENTIVE MEDICINE

695 **Regionalization of Perinatal Care**
R. LARRY MEULI, MD, and LAWRENCE J. COHEN, MD

Dr Meuli is Director of Family Health Services, Division of Health and Medical Services, and Dr Cohen is State Administrator, Division of Health and Medical Services, State of Wyoming Department of Health and Social Services, Cheyenne.

One of a series of articles from western state public health departments.

INFORMATION

698 **Diagnosis and Treatment of Myocardial Disease in Infants and Children**
RONALD D. GREENWOOD, MD

From the Division of Pediatric Cardiology, Department of Pediatrics, University of California Davis Medical Center, Sacramento.

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734 **Western State Medical Associations' Meetings**

★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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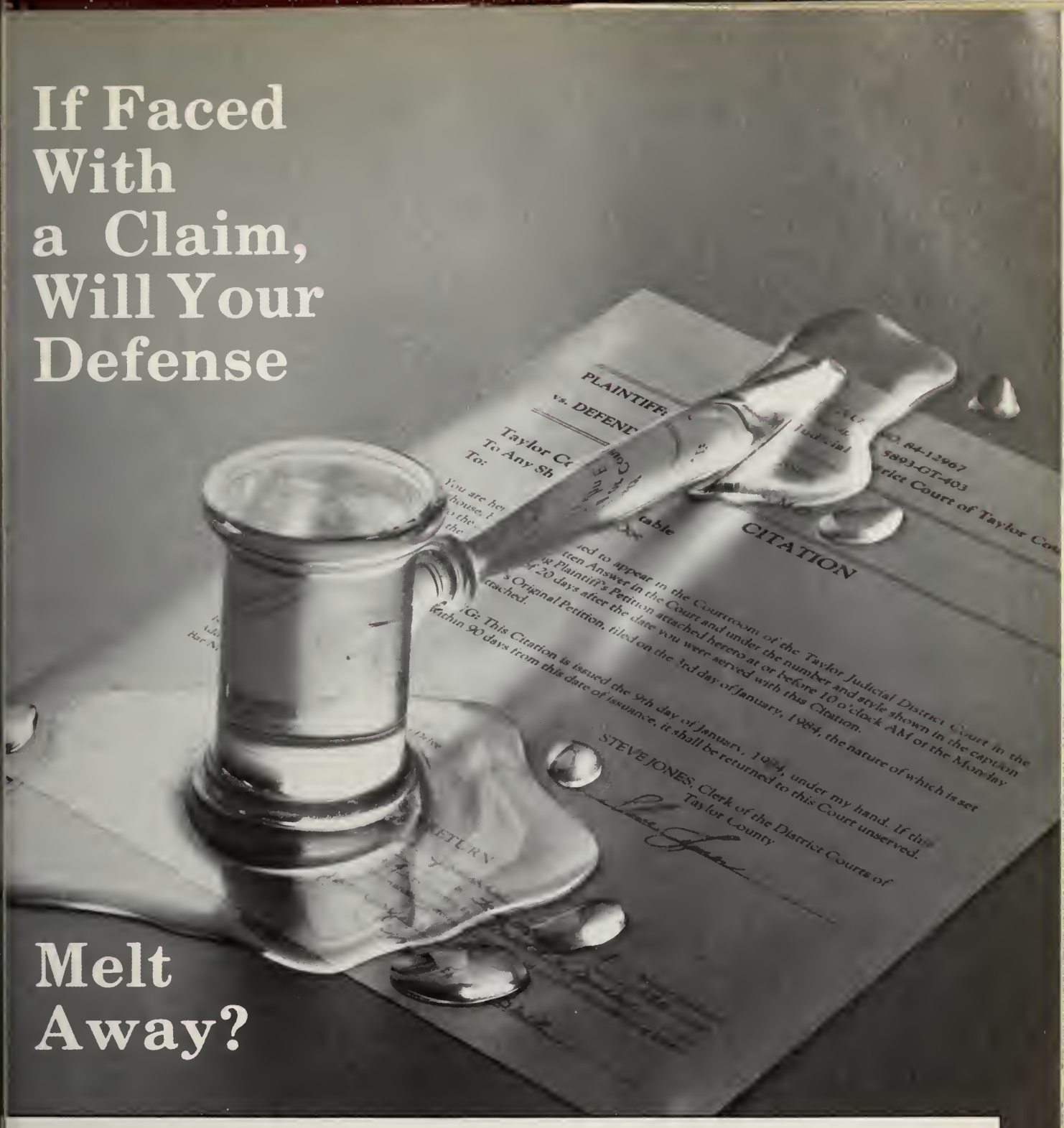

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New study reveals no interaction between

Ativan® (lorazepam) and Darvon® (propoxyphene HCl) ℞Ⓒ

In a study evaluating the influence of propoxyphene coadministration on the pharmacokinetics of the oxidatively metabolized benzodiazepines Xanax® (alprazolam) ℞Ⓒ and Valium® (diazepam) Ⓒ, and a benzodiazepine metabolized by conjugation, Ativan® (lorazepam), the following results were reported:

with Xanax, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance.[1]

in the case of Valium, propoxyphene produced a small but not statistically significant impairment of clearance.[1]

propoxyphene had no apparent effect on the distribution, half-life or clearance of Ativan.[1]

In this randomized crossover study, eight healthy male and female volunteers received single oral doses of alprazolam (1 mg), six received single IV doses of diazepam (10 mg), and five received single IV doses of lorazepam (2 mg), once in a drug-free control state and again during coadministration of propoxyphene (65 mg q6h). Consistent with previous findings, this study evidences that Ativan does not interact with drugs that undergo oxidative metabolism.[2-5] In contrast to most other benzodiazepines, Ativan does not compete for the cytochrome P-450 enzyme system.

The clinical implications of the pharmacokinetic interaction, or non-interaction, of propoxyphene with benzodiazepines are not established by this study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

Caution should also be observed when propoxyphene is prescribed for patients who use alcohol to excess.

References

1. Abernethy DR, Greenblatt DJ, Shader RI: Data on file, Wyeth Laboratories.
2. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology 79:912-916, 1980.
3. Abernethy DR, Greenblatt DJ, Divoll M, et al: Psychopharmacology 80:275-278, 1983.
4. Abernethy DR, Greenblatt DJ, Divoll M, et al. N Engl J Med 306:791-792, 1982.
5. Ochs HR, Greenblatt DJ, Abernethy DR Data on file, Wyeth Laboratories.

Wyeth Laboratories
Philadelphia, PA 19101

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Ativan® for (lorazepam) ℞Ⓒ Anxiety

See important information on following page.

The appearance of these tablets is a registered trademark of Wyeth Laboratories

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) **for** (lorazepam) **Anxiety**

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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BALANCED CALCIUM CHANNEL BLOCKADE!

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

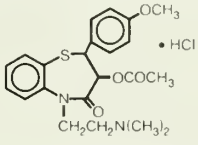
Please see full prescribing information on following page.

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm. CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LOH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LOH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy** — CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NOC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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ALLERGY AND IMMUNOLOGY

December 27-29—**Allergy and Asthma.** Hawaii Medical Association and Hawaii AAFP at Royal Lahaina Resort, Maui. Thursday-Saturday. $275. 13.5 hrs. Contact: Joe Harrison, MD, Dir., PO Box 10185, Lahaina, Maui 96761.

January 3-5—**Allergy and Dermatology.** Symposium Maui, Hawaii Medical Association, and Hawaii American Academy of Family Practice at Royal Lahaina Resort, Maui. Thursday-Saturday. 13.5 hrs. $275. Contact: Symposium Maui, Joe Harrison, MD, Director, PO Box 10185, Lahaina, Maui 96761.

January 10-12—**Allergy and Immune Diseases in Children.** Symposium Maui, Hawaii Medical Association and Hawaii American Academy of Family Practice at Royal Lahaina Resort, Maui. Thursday-Saturday. 13.5 hrs. $275. Contact: Symposium Maui, Joe Harrison, MD, Director, PO Box 10185, Lahaina, Maui 96761.

February 27-March 2—**9th Annual Course: Immunology and the Clinical Practice of Allergy.** UCSD at Vacation Village Resort, San Diego. Wednesday-Sunday. Up to 20 hrs. Contact: UCSD.

ANESTHESIOLOGY

January 10-13—**Anesthesia Update.** UCSD at Hotel Intercontinental, San Diego. Thursday-Sunday. 20 hrs. Fee: $100-$250. Contact: UCSD.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation and Childrens Hospital of Los Angeles at Los Angeles. Friday-Sunday. Contact: Wayne Herbert, MD, Program Dir., Ped. Anes. Fndn, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

December 7-9—**2nd Annual Recent Advances in Occupational Cancer Focus on Prevention.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $150.

December 12—**19th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. Contact: Linda Morgado, Med. Staff Coord., N. T. Enloe Memorial Hospital, W. 5th Ave. and The Esplanade, Chico 94926. (916) 891-7300.

January 18-19—**Urological Cancer.** USC. Friday-Saturday.

January 19—**Avoidable Cancer: Cause and Control.** UCI. Saturday. 6 hrs. Fee: $30. Contact: UCI.

(Continued on Page 601)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

Just once each day...

First-step blood pressure control with optimal simplicity

Benefits diuretics cannot offer... Once-daily INDERAL LA (propranolol hydrochloride) with its smooth 24-hour control of blood pressure provides a high degree of patient acceptance without potassium problems, plus the cardiovascular benefits of the world's leading beta blocker.

Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

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Just once each day for initial therapy in hypertension.

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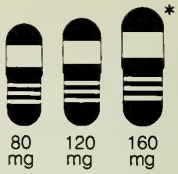
Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirements of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length and diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the platelet membrane.

Beta receptor blockade can be useful in conditions in which because of pathophysiologic or functional changes, sympathetic activity is detrimental to the patient. There are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to profracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice employing doses up to 150 mg/kg/day, there was no evidence of significant dose-related toxic effects or evidence of any correlated tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, exacerbation of intermittent claudication, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst. AYERST LABORATORIES
New York, N.Y. 10017

Just once each day for initial therapy...

(Continued from Page 597)

February 6—**Impact of Questionable Cancer: Treatments on Oncology Practice Today.** Hospital of Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, Coordinator of Symposium, 616 So. Witmer St., Los Angeles 90017. (213) 977-2352.

March 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Kona Kai Club, San Diego, Sunday. 7 hrs. Fee: $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138.

CARDIOLOGY

November 30-December 2—**Cardiovascular Disease: Non-Invasive Diagnostic Methods (Stress & Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 30-December 2—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corporation at Las Vegas. Friday-Sunday. Contact: Beverly Jacobsen, 64 Inverness Dr. E., Englewood, CO 89112. (800) 525-8651.

December 6-8—**Doppler Echocardiography.** Institute for Medical Studies at The Hotel Meridien, San Francisco. Thursday-Saturday. 15 hrs. Fee: $395. Contact: Kim Stroich, Institute for Medical Studies, 30131 Town Center Rd., Ste. 215, Laguna Miguel, CA 92677. (714) 495-4499.

December 7-9—**Cardiovascular Disease: Non-Invasive Diagnostic Method (Stress and Holter) and Cardiac Rehabilitation.** International Medical Education Corporation at San Diego. 13 hrs. Friday-Sunday. Contact: IMEC, 64 Inverness Drive E., Englewood, CO 80112. (800) 525-8651.

December 7-9—**Advances in Heart Disease 1984.** American College of Cardiology at Hyatt Regency Hotel, San Francisco. Contact: ACC, 911 Old Georgetown Rd., Bethesda, MD 20814.

January 18-19—**4th Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Sheraton Grande Hotel, Los Angeles. Friday-Saturday. 10 hrs. Contact: Masato Takahasi, MD, Division of Cardiology, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054-0700. (213) 669-2461.

January 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado Health Sciences Center at MGM Grand Hotel, Las Vegas. Friday-Sunday. 13 hrs. Contact: Med. Ed. Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

January 28-31—**3rd Annual Cardiology Update.** Institute for Medical Studies at Sheraton-Waikiki, Hawaii. Monday-Thursday. 15 hrs. Fee: $395. Contact: Kim Stroich, Institute for Medical Studies, 30131 Town Center Rd., Ste. 215, Laguna Miguel, CA 92677. (714) 495-4499.

February 8-10—**"Case Studies in Cardiology": A Cardiology Review for Clinicians.** The Presbyterian Heart Institute at Presbyterian Hospital, Albuquerque, NM. Friday-Sunday. 19 hrs. Fee: $150. Contact: Gilbert Raff, MD, (505) 242-2796

February 15-17—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center at International Hotel, Palm Springs. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 So. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

EMERGENCY MEDICINE

December 2-7—**Kauai 1984 "Current Concepts in Emergency Care."** The Institute for Emergency Medical Education and the Washington Chapter of the American College of Emergency Physicians at Kauai Surf Hotel, Kauai. Sunday-Friday. 25 hrs. Contact: Georgine Fleck, Kailani World Travel, 4192 Meridian Avenue, Bellingham, WA 98277-9951. (800) 426-2561.

December 10-14—**Postgraduate Institute for E.R. Physicians, Symposium II.** UCSD at La Jolla Village Inn, La Jolla. Monday-Friday. (619) 452-3940.

January 14-18—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 13-36 hrs. Fee: $200-$675. Contact: UCSD.

January 19-26—**Management of Traumatic Emergencies.** UCSD at Kona Surf Resort, Kona, HI. Sunday-Sunday. 21 hrs. Fee: $315-$430. Contact: UCSD.

January 28-30—**Trauma: 1985.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 20 hrs.

February 24-March 1—**Emergency Medicine: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Sunday. Contact: UCD.

February 25-28—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: USC.

(Continued on Page 602)

SNOWBIRD CONFERENCES

Sponsored by
University of Utah School of Medicine

February 25-March 1, 1985
ADVANCES IN INTERNAL MEDICINE
$275 fee, CME Credit Available

March 4-8, 1985
MEDICAL AND SURGICAL ADVANCES IN GASTROENTEROLOGY
$275 fee, CME Credit Available

PARK CITY CONFERENCE

March 18-22, 1985
NUTRITION IN CONTEMPORARY MEDICINE
$275 fee, CME Credit Available

Information/Registration: Jennifer Fossum
Division of Gastroenterology
University Medical Center
Salt Lake City, UT 84132
(801) 581-3581

2nd ANNUAL MEETING & SEMINAR

of the
American Association
of Orthopaedic Medicine
The Neurobiologic Foundations of Orthopaedic Medicine
Special Guests: Professor Barry Wyke & Dr. John Mennell

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Maricopa Medical Center
Department of Anesthesiology

Scottsdale, AZ – Feb. 27–Mar. 3, 1985

Didactic and hands-on sessions in evaluation and management.
23 Hours CME I (AMA & AOA) anticipated

For Information Contact:
Kent L. Pomeroy, M.D., Secretariat
AAOM
926 E. McDowell, Suite 202
Phoenix, AZ 85006

CONTINUING MEDICAL EDUCATION

(Continued from Page 601)

INTERNAL MEDICINE

November 16-18—**Pulmonary Medicine and Office Spirometry for P.C. Physician.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday.

November 30-December 2—**Fluid and Electrolytes.** Cedars-Sinai Medical Center at La Quinta Hotel, La Quinta. Friday-Sunday. Contact: Lore Kahane, Cedars-Sinai Medical Center, 8700 Beverly Blvd. #2049, Los Angeles 90048. (213) 855-5000.

December 7-8—**Common Rheumatic Diseases for the Clinician.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday. 15 hrs. Contact: UCD.

December 11-13—**7th Annual Midwinter Meeting of the American Endocurietherapy Society** at Wailea Beach Hotel, Maui. Tuesday-Thursday. $250. Contact: AES, 1245 Wilshire Blvd., Ste. 217, Los Angeles 90017.

January 9—**Urology—The Prostate.** LLU at LLU Medical Center. Wednesday. Contact: LLU.

January 24-26—**Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West, San Diego. Thursday-Saturday. 18 hrs. Fee: $300. Contact: UCSD.

January 24-26—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West, San Diego. Thursday-Saturday. 18 lhrs. Contact: UCSD.

February 8-9—**Infectious Disease: Clinical Update.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. Contact: UCD.

February 12-17—**18th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Tuesday-Sunday. Contact: UCSF.

February 17-22—**Advanced Problems in Infectious Diseases and Toxicology.** UCSD at Continental Inn, Aspen. Sunday-Friday. 21 hrs. Fee: $315-$430. Contact: UCSD.

February 21-24—**Federation of Societies of Neurological Science.** FSNS at Hotel Intercontinental, San Diego. Thursday-Friday. 18 hrs. Contact: James Grisolia, MD, 4020 5th Ave, Ste. 404, San Diego 92138. (619) 297-1155.

March 18-20—**Gastroenterology Course.** UCSF at Yosemite. Monday-Wednesday. Contact: UCSF

1985 CME Cruise/Conferences on Legal-Medical Issues

Accredited for 20–24 CME CAT. 1 Credits by The Suffolk Academy of Medicine
Approved for 20–24 AAFP Prescribed Credits

The programs listed below were scheduled prior to 12/31/80 and conform to IRS tax deductibility requirements under Sec. 602 of the Tax Reform Act-P.L. 94-445, effective 1/1/77, with the exception of the Hawaiian Conferences, which conform to the requirements of P.L. 97-424.

24 CME CREDITS

- ☐ *Jan. 9–19 (from Ft. Lauderdale, FL)
  10 day Caribbean - TSS FAIRWIND
- ☐ *Mar. 30–Apr. 10 (from Los Angeles, CA)
  11 day Mexican Riviera - TSS FAIRSKY
- ☐ *July 8–20 (from San Francisco, CA)
  12 day Alaska/Canada - TSS FAIRSKY

24 CME CREDITS

- ☐ *July 24–Aug. 3 (from Ft. Lauderdale, FL)
  10 day Caribbean - TSS FAIRWIND
- ☐ Aug. 24–Sept. 5 (from Athens, Greece)
  12 day Mediterranean - PACIFIC PRINCESS

20 CME CREDITS

- ☐ Monthly 7 day cruise/seminars from Honolulu, HI on a variety of medical topics.
  SS CONSTITUTION, SS INDEPENDENCE

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CONTINUING MEDICAL EDUCATION

OBSTETRICS AND GYNECOLOGY

December 13-15—**Gynecologic Surgery.** The American College of OB/GYN at Hyatt Regency Hotel, Los Angeles. Thursday-Saturday. Contact: ACOG, Patience A. Schenck, 600 Maryland Ave., SW, Washington, DC 20024. (202) 638-5577.

February 3-7—**OB/GYN Update: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: UCD.

February 9-10—**Los Angeles OB/GYN Forum.** Los Angeles OB/GYN Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. 10 hrs. Fee: $80. Contact: Director of Medical Education, LA OB/GYN Society, 5820 Wilshire Blvd, #500, Los Angeles, CA 90036. (213) 937-5514.

February 9-16—**13th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki, HA. One week. 20 hrs. Contact: Arlene Rogers, OSUH, Department of Anesthesiology, 410 W. 10th Ave, Columbus, OH 43210. (614) 421-8487

February 11-15—**San Diego Abdominal and Obstetrical Imaging Symposium Update.** UCSD at Hotel Intercontinental, San Diego. Fee: $425. Contact: UCSD.

February 16-23—**Perinatal Medicine.** USC at Royal Lahaina, Maui, HI. One week.

February 23—**OB/GYN.** UCSF at Fresno. Saturday. Contact: UCSF.

March 2-9—**6th Annual Symposium on Current Topics in Obstetrics.** UCI at Aspen, Colorado. One week. 23 hrs. Contact: UCI.

OPHTHALMOLOGY

November 30-December 1—**Phacoemulsification, Extracapsular Cataract Surgery & Intraocular Lenses.** Jules Stein Eye Institute at Los Angeles. Friday-Saturday.

December 7-8—**Glaucoma Management: The State of the Art.** UCSF at Hyatt Regency Hotel, San Francisco. Friday-Saturday.

December 8—**Ophthalmology Association Clinical Meeting.** Jules Stein Eye Institute at Los Angeles. 5

(Continued on Page 606)

In clinical anxiety,

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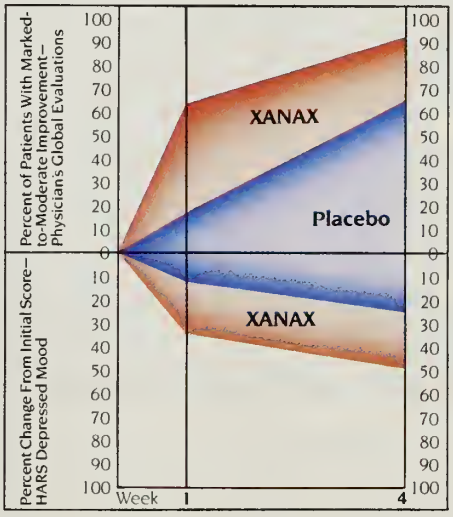
Kalamazoo, Michigan 49001 USA

depressive symptoms are part of the picture in 7 out of 10 geriatrics.

The geriatric profile of XANAX can help.

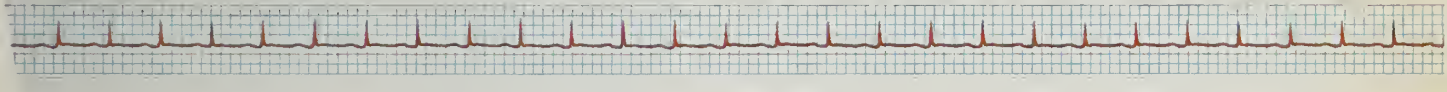
In a recent clinical study* of 83 geriatric patients with clinical anxiety, 73% were diagnosed as also having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the overall Hamilton Anxiety Rating Scale Total Score by significantly reducing individual items including depressed mood (see Figure).


Percent of Patients With Marked-to-Moderate Improvement—Physician's Global Evaluations
Percent Change From Initial Score—HARS Depressed Mood
XANAX
Placebo
XANAX
100 90 80 70 60 50 40 30 20 10 0
10 20 30 40 50 60 70 80 90 100
Week 1 4

A desirable profile of clinical advantages

- **Rapidly relieves** the symptoms of anxiety including depressed mood
- **No clinically significant ECG changes** over the course of therapy



- **Relieves the symptoms of insomnia** significantly better than placebo
- Drowsiness is the most frequently reported adverse effect
- **Simple geriatric dosage**—0.25 mg, two or three times daily

*Data on file. The Upjohn Company.

Please see next page for brief summary of prescribing information.

Xanax® 0.25 mg Tablets

alprazolam C-IV

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests.* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

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CONTINUING MEDICAL EDUCATION

(Continued from Page 603)

hrs. Saturday. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

January 24-25—**YAG Laser Source.** UCSD at UCSD Medical Center. Thursday-Friday. 12 hrs. Contact: UCSD.

February 8-10—**5th Annual Current Concepts in Ophthalmology 1985.** UCSD at Hotel Del Coronado, San Diego. Friday-Saturday. 15 hrs. Contact: UCSD.

March 14-15—**Modern Surgical Techniques and Their Effects of the Cornea.** Pacific Medical Center at Clift Hotel, San Francisco. Thursday-Friday. Contact: Pacific Medical Center, Continuing Education, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

PATHOLOGY

February 3-6—**12 Annual Course in Genitourinary Pathology.** UCI at Memorial Medical Center, Long Beach. Sunday-Wednesday. 36 hrs. Contact: UCI.

PEDIATRICS

November 16-19—**Clinical Pediatrics.** California Chapters 1, 2 & 3 American Academy of Pediatrics at Las Vegas. Friday-Monday. Contact: Eve Black, Exec. Sec., PO Box 2134, Inglewood 90305. (213) 757-1198.

December 3—**Issues in Perinatal Care.** UCSF. Monday.

December 6-9—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Rancho Mirage. 14 hrs. Thursday-Sunday.

January 25-26—**Advanced Fetal Heart Rate Monitoring Seminar.** UCI at South Coast Plaza Hotel, Costa Mesa. Friday-Sunday. 12 hrs. Contact; UCI.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 25-27.

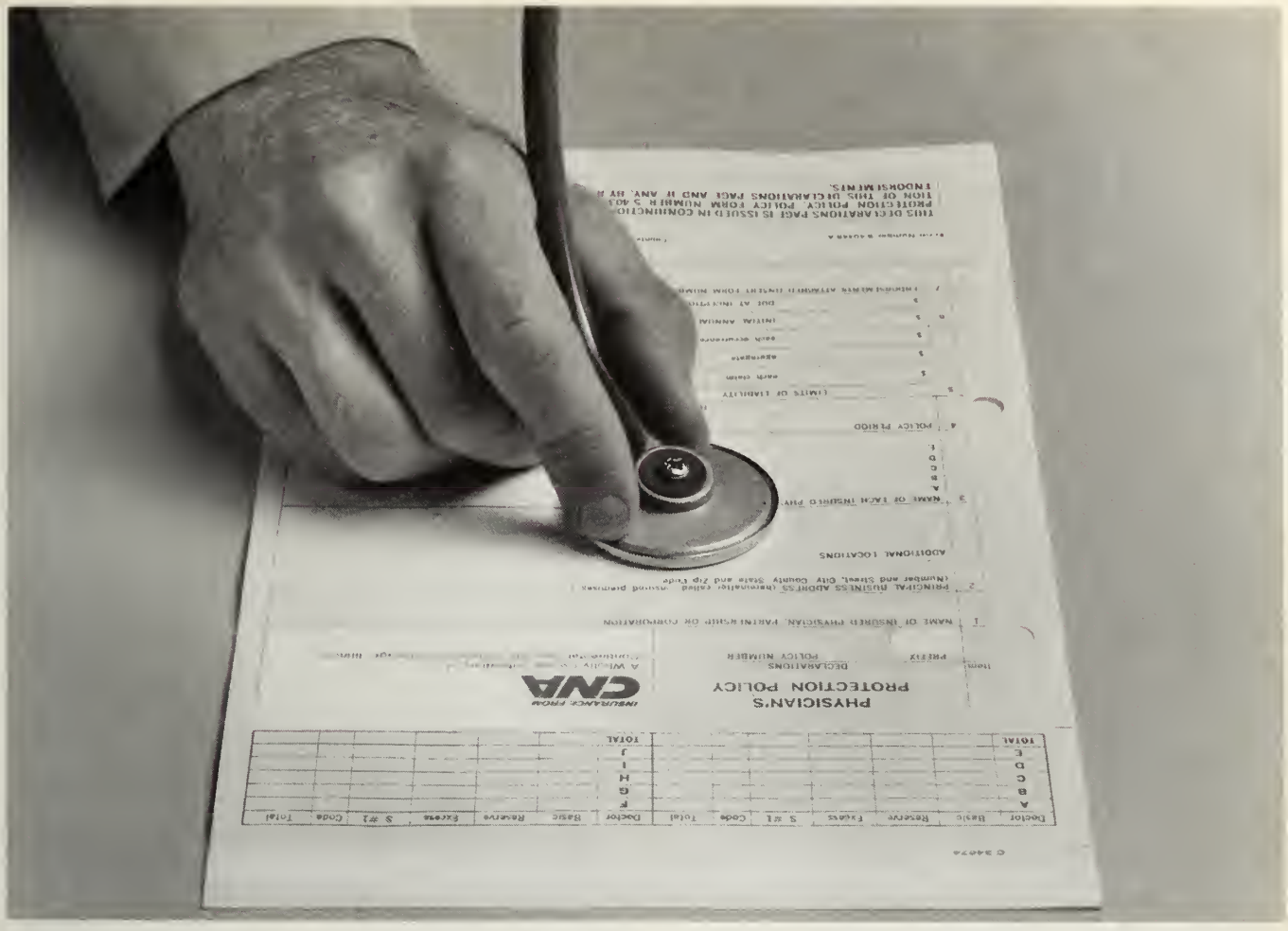
February 2-9—**Pediatric Emergencies.** UCSD at Snowbird Resort, Utah. One week. 21 hrs. Fee: $315-$350. Contact: UCSD.

March 7-9—**Brain Insults in Infants and Children: Pathology, Evaluation, Diagnosis and Acute Management.** UCSD at Holiday Inn Embarcadero, San Diego. 17 hrs. Contact: UCSD.

PSYCHIATRY

January 27-February 1—**Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. Contact: UCD.

(Continued on Page 704)



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The Physicians Protection Program is underwritten by Continental Casualty Company or CNA Casualty of California, two of the CNA Insurance Companies.

The Physicians Protection Program is available to individual physicians in Washington and Idaho and through association sponsored programs in California.

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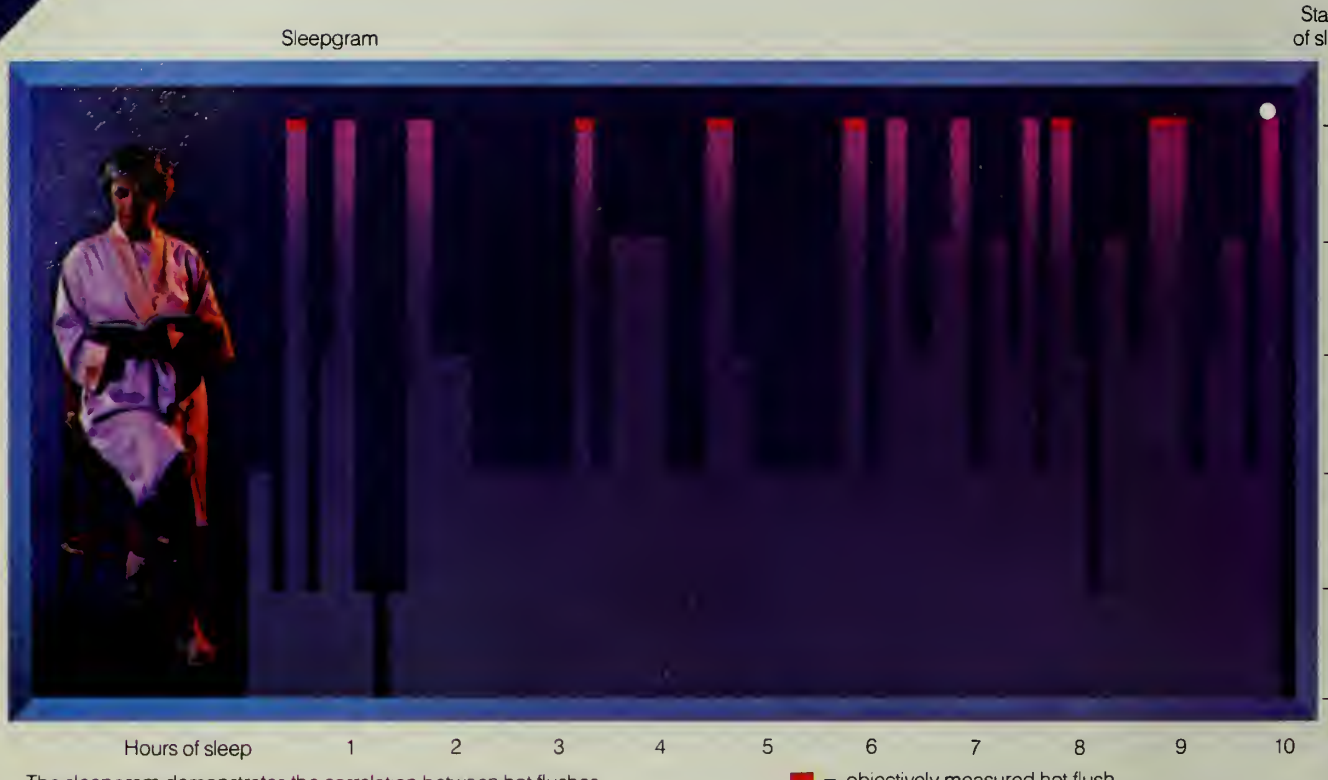
For All the Commitments You Make

0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISRUPTIVE PATTERN OF VASOMOTOR SYMPTOMS



The sleepgram demonstrates the correlation between hot flushes and waking episodes that can disrupt the menopausal woman's sleep night after night. —adapted from Erlik et al, p 1742.[1]

= objectively measured hot flush
o = arousal of patient by investigator at end of the study
W = Waking
R = Rapid Eye Movement (REM)

EFFECTIVE TREATMENT

Hot flushes, with associated immediate-waking episodes, can occur several times a night—severely disrupting the menopausal patient's sleep.[2] The symptoms may also appear during the day and seriously disrupt the patient's life.

Scientific evidence has shown that the symptoms are not purely subjective.[2] In one study, nearly all objectively recorded hot flushes during sleep were associated with immediate waking episodes.[1] They're the most common cause for which menopausal patients seek medical attention.[2] At least 75% of menopausal women experience the symptoms, which persist for over one year in 80% of those afflicted. But 25% to 50% of the women suffer longer than five years.[3]

PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) therapy is effective in reducing the severity and frequency of symptomatic attacks and eliminating them altogether. When moderate to severe vasomotor symptoms are chronically disruptive, provide relief with PREMARIN.

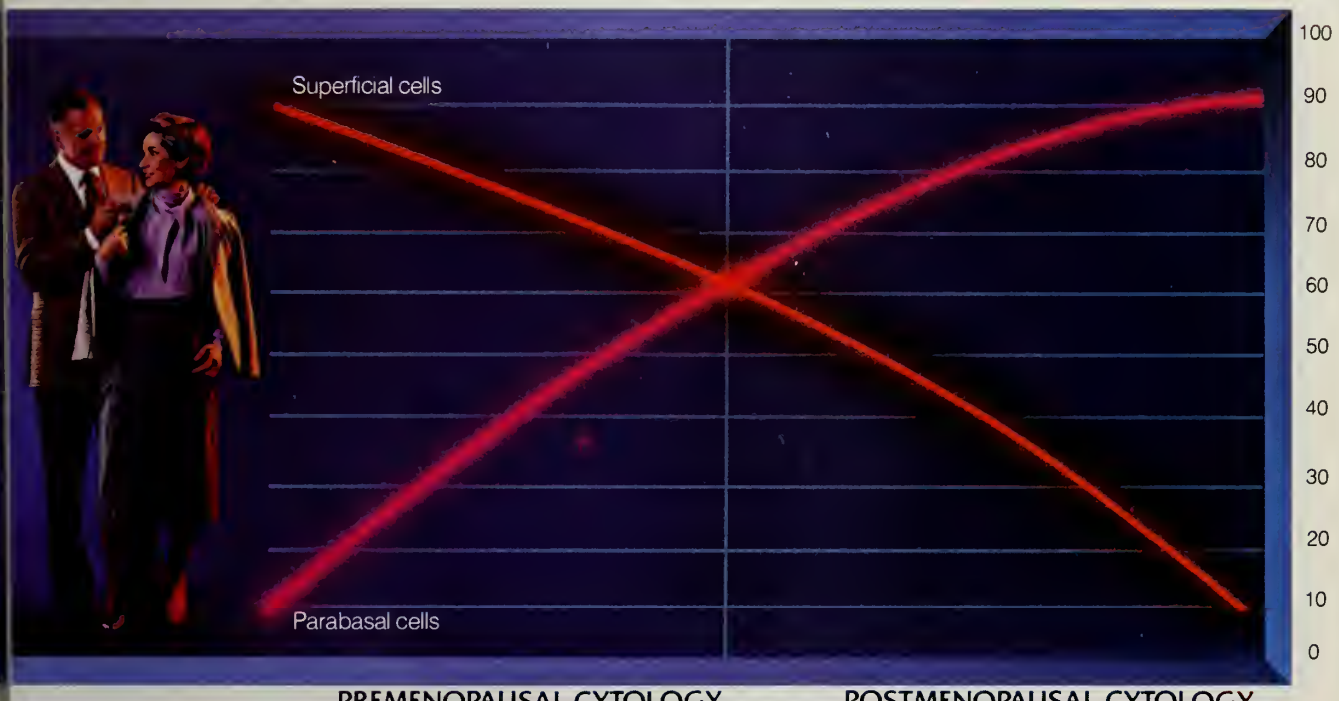
FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

THE DISTRESSING CONSEQUENCES OF ATROPHIC VAGINITIS



PREMENOPAUSAL CYTOLOGY POSTMENOPAUSAL CYTOLOGY

Estrogen levels—to diagnose estrogen deficiency or monitor replacement therapy—are revealed by cytologic examination of vaginal smears. Since estrogen is essential for their maturation, the predominance of superficial cells is an indicator of high estrogen levels—characteristic of the younger woman. Postmenopausal estrogen depletion is characterized by a corresponding decline in superficial cells and a significant rise in parabasal cells.

THERAPY AS SPECIFIC AS THE PROBLEM

Cytologic examination of vaginal smears can be used as part of the diagnosis of estrogen deficiency.[4] Topical application of PREMARIN® (Conjugated Estrogens, U.S.P.) Vaginal Cream may be appropriate.[2] Therapy is concentrated just where it is needed—in the vaginal environment.

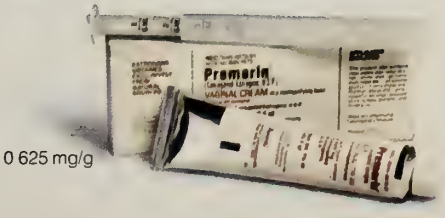
PREMARIN Vaginal Cream has been shown to significantly increase the number of superficial cells in menopausal women within one month.[5] It stimulates epithelial proliferation of the vulva and vagina—returning them to a healthier state in one or two weeks. Symptoms such as dryness, burning, and itching are relieved.[2] Vaginal pH reverts to normal acidity. Normal flora are reestablished, reducing the possibility of local or general infection. Dyspareunia, associated with atrophic vaginitis, is also alleviated.

When vaginal atrophy is the only consequence of estrogen deficiency, PREMARIN Vaginal Cream helps return the vaginal environment to its premenopausal state.

Please see last page for brief summary of prescribing information.

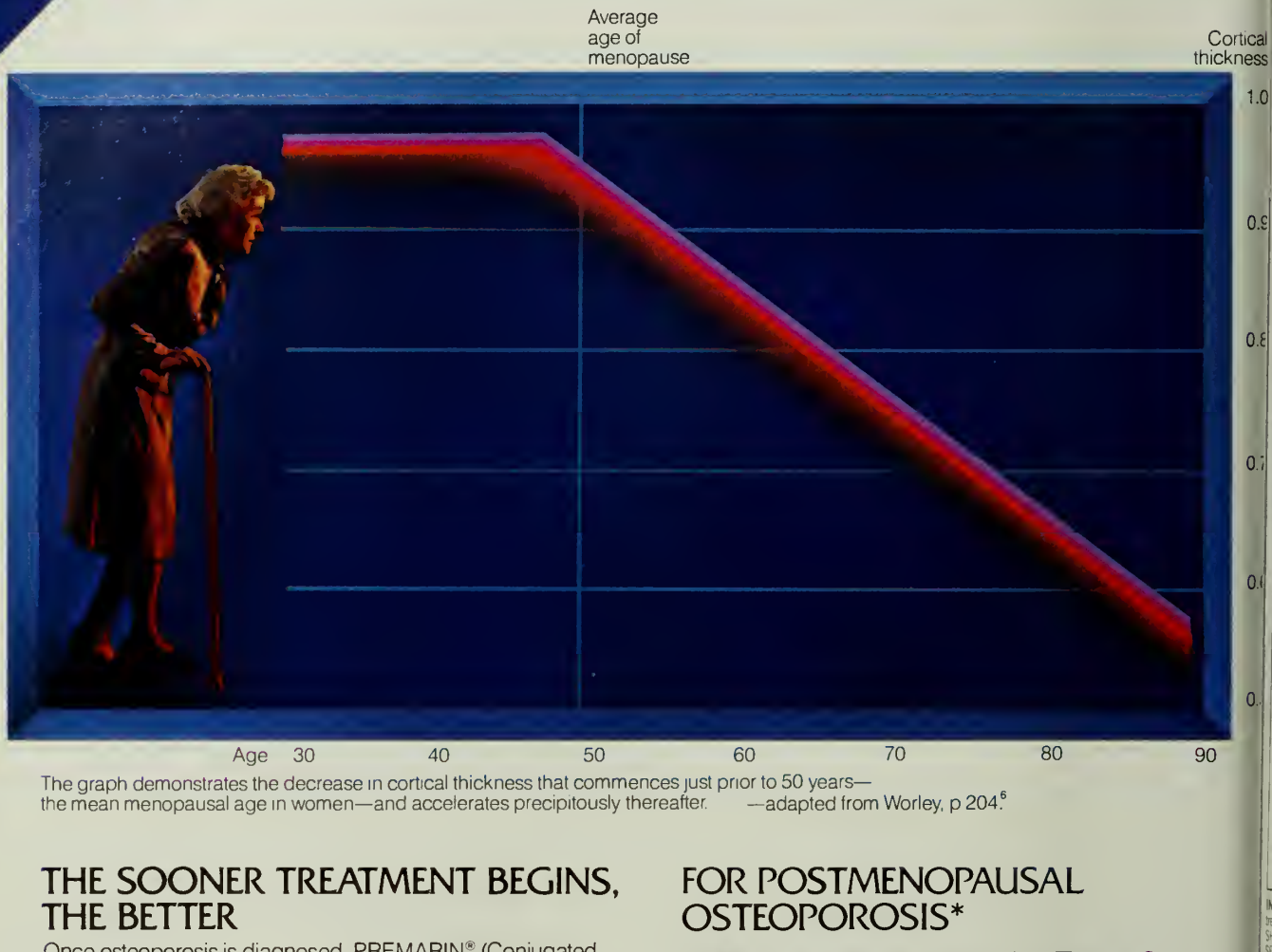
FOR ATROPHIC VAGINITIS

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.9 MG TABLET
ADDED DOSAGE
PRECISION

THE DISABLING COURSE OF OSTEOPOROSIS



The graph demonstrates the decrease in cortical thickness that commences just prior to 50 years—the mean menopausal age in women—and accelerates precipitously thereafter. —adapted from Worley, p 204.[6]

THE SOONER TREATMENT BEGINS, THE BETTER

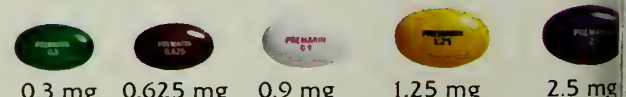
Once osteoporosis is diagnosed, PREMARIN® (Conjugated Estrogens Tablets, U.S.P.) may prove highly beneficial in retarding further bone loss.* PREMARIN treatment should be initiated promptly after osteoporosis is detected to help arrest bone resorption throughout the skeleton, including long bones, pelvic bones, and vertebrae—which are particularly susceptible to trauma. Along with PREMARIN, evaluation of diet, calcium intake, and physical exercise is recommended.

Watching for early warning signals of osteoporosis in high-risk patients is vital. These individuals can be identified by a composite of certain characteristics: white race, slender, slight build, premature or surgical menopause, sedentary life-style, family history of the disease, as well as high caffeine intake, cigarette smoking, and alcoholism.

Osteoporosis affects one of four postmenopausal women.[7] Based on 1980 census data which reports that 23.3 million women were in the 45–64 year age group, over 5 million women may suffer from this condition.[8] Once the damage is done, it is too late to restore bone that has been lost. That's why scientific literature stresses the need for early detection.[9] After osteoporosis is confirmed, early intervention with PREMARIN may be the best course to take.

FOR POSTMENOPAUSAL OSTEOPOROSIS*

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating postmenopausal osteoporosis

Please see last page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPDRTED TO INCREASE THE RISK DF ENDDMETRIAL CARCINDMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTRDGENS SHOULD NDT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogens, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum, hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days.* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube. **8934/984**

REFERENCES: 1. Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. 2. Judd HL, Meldrum DR, Deftos LJ, et al: Estrogen replacement therapy: Indications and complications. *Ann Intern Med* 1983;98:195-205. 3. Estrogen replacement therapy. *ACOG Tech Bull*, June 1983, pp 1-5. 4. Ayers LJ: The maturation index: A test for estrogen deficiency. *Female Patient* 1982;7:32-36. 5. Semmens JP, Wagner G: Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-448. 6. Worley RJ: Age, estrogen, and bone density. *Clin Obstet Gynecol* 1981;24:203-218. 7. Gordan GS, Pinchuj Roof BS, et al: Postmenopausal osteoporosis. *Am Fam Physician* 1973;8:74-83. 8. US Bureau of the Census, *Statistical Abstract of the United States* 1982-83, ed 103, Washington, DC: US Dept of Commerce, 1982, p 25. 9. Mallette LE: Osteoporosis: Approaching treatment with optimism. *Postgrad Med* 1982;72:271-278.

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

It Pays to Save Potassium
K+
Potassium-Sparing
DYAZIDE
Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.
In Hypertension*‡ When You Need to Conserve K+
Serum K+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide, dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

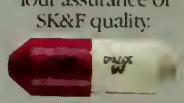
Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

The unique red and white Dyazide* capsule: Your assurance of SK&F quality.



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Clinical Investigation

Pneumocystis carinii Pneumonia Treated With α-Difluoromethylornithine

A Prospective Study Among Patients With the Acquired Immunodeficiency Syndrome

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Pneumocystis carinii *pneumonia is a protozoal infection that, in the setting of acquired immunodeficiency syndrome (AIDS), is often lethal and unresponsive to conventional therapy with trimethoprim-sulfamethoxazole or pentamidine. In the present study, we have prospectively assessed the use of α-difluoromethylornithine (DFMO), an inhibitor of polyamine biosynthesis, in the treatment of* P carinii *pneumonia in patients with AIDS who were intolerant or unresponsive to conventional drugs. Improvement by both clinical and objective criteria was observed in six patients who completed six to eight weeks of DFMO therapy. Expansion of these early trials of DFMO is warranted.*

(Golden JA, Sjoerdsma A, Santi DV: *Pneumocystis carinii* pneumonia treated with α-difluoromethylornithine—A prospective study among patients with the acquired immunodeficiency syndrome [Clinical Investigation]. West J Med 1984 Nov; 141:613-623)

Pneumocystis carinii, although a ubiquitous protozoan, causes disease only in immunocompromised hosts.[1-3] *P carinii* pneumonia is the most common lethal infection in patients with acquired immunodeficiency syndrome (AIDS).[1,4,5] Although *P carinii* pneumonia usually responds to treatment with trimethoprim-sulfamethoxazole (TMP-SMX) or pentamidine in patients who do not have AIDS, these drugs are often inadequate or cause severe toxic reactions when used to treat *P carinii* pneumonia in patients who do have AIDS.[6-13] For such patients there is an immediate need for a safe and effective agent for treating *P carinii* pneumonia.

α-Difluoromethylornithine (DFMO) reduces intracellular polyamines by specific and irreversible inhibition of ornithine decarboxylase. Although polyamines are ubiquitous in living cells and are important in cell growth and replication, DFMO is well tolerated and remarkably nontoxic in animals and humans.[14,15] DFMO is an impressive antiprotozoan agent that has been used with dramatic success to treat infection by African trypanosomes in both animals and humans.[14,16,17] DFMO has also been shown to inhibit the protozoa *Eimeria tenella*, the exoerythrocytic form of *Plasmodium berghei*, *Trichomonas vaginalis* and *Giardia lamblia*.[14,18-20] Because *P carinii* is generally considered to belong to the protozoan subkingdom,[9,21] we felt that DFMO might be useful in treating *P carinii* pneumonia.

DFMO has also exhibited effects in the laboratory setting that might, in principle, benefit patients with AIDS. First, patients with AIDS are frequently infected with cytomegalovirus, an agent that itself may contribute to immunosuppression.[22,23] DFMO reportedly blocks the replication of human cytomegalovirus in cell cultures of human diploid fibroblasts.[24] Second, AIDS is fundamentally a disorder of the immune system. Improving immunocompetence in AIDS patients would be considerably important.[25] Recently, polyamine synthesis has been shown to play a role in the production of suppressor T cells, and mice treated with DFMO have had an increase in the ratio of helper-to-suppressor T cells.[26]

In this report, we describe the results of an initial clinical trial that used DFMO to treat *P carinii* pneumonia in six AIDS patients who were refractory or intolerant to

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Presented in part at the 97th Annual Meeting of the Association of American Physicians, May 1984.

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ABBREVIATIONS USED IN TEXT

AIDS—acquired immunodeficiency syndrome
DFMO—α-difluoromethylornithine
Pao_2—partial pressure of oxygen
$Paco_2$—partial pressure of carbon dioxide
TMP-SMX—trimethoprim-sulfamethoxazole

TMP-SMX and pentamidine. Our findings suggest that DFMO may be an important new agent for the treatment of *P carinii* pneumonia in patients with AIDS.

Methods

The protocol for assessing DFMO therapy for *P carinii* pneumonia was approved by the University of California Committee on Human Research. All patients who participated in the study gave informed consent. Only patients with AIDS and a diagnosis of *P carinii* pneumonia confirmed by biopsy were eligible. AIDS was defined as the occurrence of a life-threatening opportunistic infection or Kaposi's sarcoma in patients younger than 60 years with no known cause for immunodeficiency.[4,5] Other eligibility criteria were refractoriness or life-threatening toxic reactions to pentamidine and TMP-SMX. Refractoriness was defined as a worsening clinical course, including dyspnea, elevated temperature, increased infiltrates on roentgenograms of the chest and worsening arterial blood-gas values. In addition, patients were eligible only if they were expected to survive for at least two weeks when they were deemed refractory to treatment.

The initial dose of DFMO was 6 grams per sq m of body surface area per day, divided in three orally given doses, for eight weeks. In the event of toxicity, administration of the drug was to be discontinued. If the specific toxic manifestation disappeared when DFMO therapy was discontinued, the therapy was to be restarted at a lower dosage: 4 grams per sq m per day given orally.

To assess the benefit and toxicity of DFMO, baseline and follow-up data were collected from the following sources: medical history, physical examination, routine blood analysis as well as enumeration of helper and suppressor T-cell subsets,[27] arterial blood gas determinations (specimens were taken while the patient breathed room air), chest roentgenograms, audiologic evaluation, gallium lung scan and fiberoptic bronchoscopy. Gallium lung scans were done 48 hours after intravenous injection of gallium 67 citrate at 100 μCi per kg. Pulmonary gallium uptake was evaluated as follows: grade 1, less than or equal to that in the adjacent soft tissue; grade 2, greater than that in adjacent soft tissue; grade 3, equal to that in the liver, or grade 4, greater than that in the liver. Resolution from grade 3 or 4 diffuse gallium uptake to grade 1 or focal grade 2 was interpreted as successful therapeutic response.[28-33] Flexible fiberoptic bronchoscopy was carried out by methods previously described.[34] Bronchoalveolar lavage specimens were taken by wedging the bronchoscope into a segmental bronchus and instilling five aliquots of 20 ml of normal saline to obtain a bronchoalveolar lavage sample of at least 30 ml.

Results

Nine patients participated in the study between July 1983 and July 1984. Two patients elected to stop all supportive measures and therapy after one day of treatment with DFMO and died within 72 hours. A third patient was treated with DFMO for four days but he subsequently elected to resume pentamidine therapy, which had resulted in thrombocytopenia five months earlier; he had a slow and incomplete recovery during the subsequent month of pentamidine therapy with no recurrent thrombocytopenia. Six patients completed six to eight weeks of DFMO therapy.

Reports of Cases

Patient 1

A 34-year-old white homosexual man was admitted to hospital on July 18, 1983, after two weeks of progressive dyspnea and nonproductive cough. The only abnormality on physical examination was oral mucosal candidiasis. Arterial

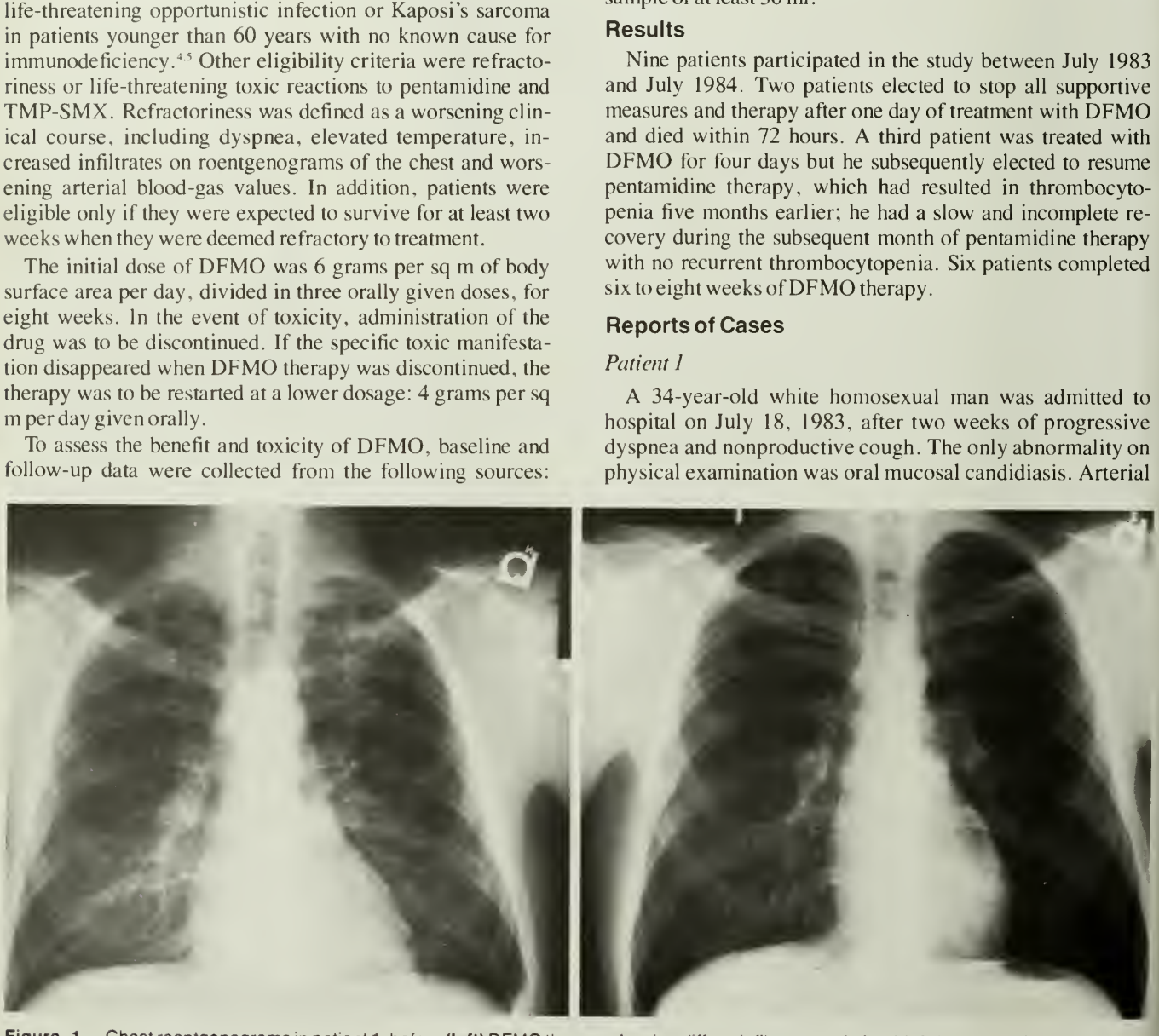

Figure 1.—Chest roentgenograms in patient 1, before **(left)** DFMO therapy showing diffuse infiltrates and after **(right)** 25 days of DFMO therapy showing resolved infiltrates.

blood gases (room air) were as follows: partial pressure of oxygen (Pao_2) 68 mm of mercury, partial pressure of carbon dioxide ($Paco_2$) 39 mm of mercury and pH 7.44. A chest roentgenogram showed bilateral infiltrates, and transbronchial biopsy showed *P carinii* pneumonia.

The patient was initially treated with TMP-SMX. After nine days a diffuse erythematous rash developed and the patient became febrile; TMP-SMX was replaced by pentamidine therapy. Four days later the infiltrates on the chest roentgenogram showed some resolution, and both the fever and diffuse rash diminished. However, on day 7 of pentamidine therapy, the patient's temperature again rose as high as 40°C (104°F) and a chest roentgenogram showed increased infiltrates (Figure 1). Arterial blood gas studies done while the patient was breathing room air showed Pao_2 50 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.44; while he was breathing 5 liters of oxygen per minute via nasal prongs, Pao_2 was 65 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.35. On day 8 of pentamidine therapy, bronchoscopy confirmed the persistence of *P carinii* pneumonia. At this time the patient was considered unresponsive to pentamidine therapy: he had increased temperature, worsening arterial blood gas values, increased infiltrates on chest roentgenograms and grade 4 diffuse uptake on a gallium scan (Figure 2). TMP-SMX therapy was reinstituted but caused an immediate hypotensive reaction that required treatment with dopamine. On August 8, DFMO therapy was initiated. By the fourth day of DFMO therapy, the patient became less dyspneic; his temperature returned to normal and remained so throughout the rest of his hospital stay. After one week of DFMO therapy, findings on chest roentgenograms improved and subsequent chest roentgenograms showed progressively less infiltrate (Figure 1). Arterial blood gas values (room air) also improved after one week of therapy: Pao_2 92 mm of mercury, $Paco_2$ 41 mm of mercury and pH 7.43. The patient was discharged from hospital after 11 days of DFMO therapy.

As an outpatient, after a total of 30 days of treatment with DFMO, the patient remained free of dyspnea on exertion, and the chest roentgenogram was normal. A gallium lung scan showed resolution to grade 1 (Figure 2), and arterial blood gas values (room air) were Pao_2 90 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.37. Transbronchial biopsy showed no evidence of *P carinii* pneumonia and no *P carinii* cysts were evident in the bronchoalveolar lavage specimen. Cytomegalovirus was not cultured from the lung in either the initial or this post-DFMO bronchoscopic evaluation. The patient arbitrarily decided to stop DFMO therapy after seven weeks.

DFMO may have caused hematologic side effects. Although the hemoglobin level and the platelet count remained unchanged, the leukocyte count fell from 6,100 per μl before DFMO therapy to 2,200 per μl after 14 days of therapy. The leukocyte count later increased spontaneously but never exceeded 3,000 per μl during the course of therapy. During the seven months after therapy, the leukocyte count remained in the range of 2,500 to 3,000 per μl. Also, serial audiologic evaluations, including a study done one month after the completion of DFMO therapy, showed normal hearing acuity.

Initial immunologic evaluation on July 1, before DFMO therapy, showed 48% T cells (normal, 65% to 85%) with 12% helper T cells (normal, 40% to 60%) and 28% suppressor T cells (normal, 20% to 40%); the helper:suppressor ratio was 0.4 (normal, 1.2 to 2.3). Evaluation after DFMO therapy showed 53% T cells, with 14% helper T cells, 42% suppressor T cells and a helper:suppressor ratio of 0.34. The patient was asymptomatic after discontinuation of DFMO therapy for the seven months he was followed by one of the authors (J.G.).*

*One year following DFMO therapy patient 1 was admitted to a community hospital with fulminant *P carinii* pneumonia. Although he was not a candidate for our protocol because of the severity of his pneumonia, his physician treated him with DFMO on a compassionate basis. The patient's condition rapidly deteriorated and he died. No autopsy was carried out.

Figure 2.—Gallium lung scans, posterior view, in patient 1, before **(left)** DFMO therapy showing diffuse gallium uptake and after **(right)** one month of DFMO therapy showing resolution of gallium uptake.

Patient 2

A 36-year-old white homosexual man was admitted to hospital on September 23, 1983, because of dyspnea for two days and nonproductive cough for one week. The patient also had had three weeks of watery diarrhea and fever associated with an 11-kg (25-lb) weight loss. On physical examination, he appeared to be in a toxic condition with acute respiratory distress, breathing 40 times per minute, and had a temperature of 38.5°C (101.3°F); oral examination showed mucosal candidiasis. Arterial blood gas values (room air) were Pao_2 56 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.46. A chest roentgenogram showed bilateral hazy infiltrates.

Because the patient was too ill for bronchoscopy, a presumptive diagnosis of *P carinii* pneumonia was made. Pentamidine therapy was initiated because the patient had previously had a severe Steven-Johnson reaction to sulfa-drug therapy. A bronchoalveolar lavage specimen taken 48 hours after admission showed *P carinii* cysts. Also, cytomegalovirus was cultured from the lavage specimen. Transbronchial biopsy was not done at this time because the patient was too ill and uncooperative.

The patient remained in a toxic condition with temperatures of 38.5°C to 39°C (101°F to 102°F) during six days of pentamidine therapy. On day 6 of the therapy, roentgenogram of the chest showed that the pneumonia had progressed since the patient was admitted (Figure 3), and arterial blood gas values (room air) had worsened, with Pao_2 35 mm of mercury, $Paco_2$ 34 mm of mercury and pH 7.45. A gallium lung scan showed diffuse grade 4 uptake (Figure 4).

In view of the progressive *P carinii* pneumonia, the patient was considered unresponsive to pentamidine therapy. On September 28, oral DFMO therapy was initiated. Because of persistent diarrhea, on October 5 the drug was administered intravenously at 4 grams per sq m per day in three divided doses; on October 8, the dosage was increased to 5 grams per sq m per day.

On day 3 of DFMO therapy, the patient was subjectively improved. He became afebrile on day 6 and his gas exchange also improved; arterial blood gas values (room air) were Pao_2 54 mm of mercury, $Paco_2$ 39 mm of mercury and pH 7.42. With continued DFMO therapy, the patient had progressively less dyspnea, his temperature did not rise above 38°C

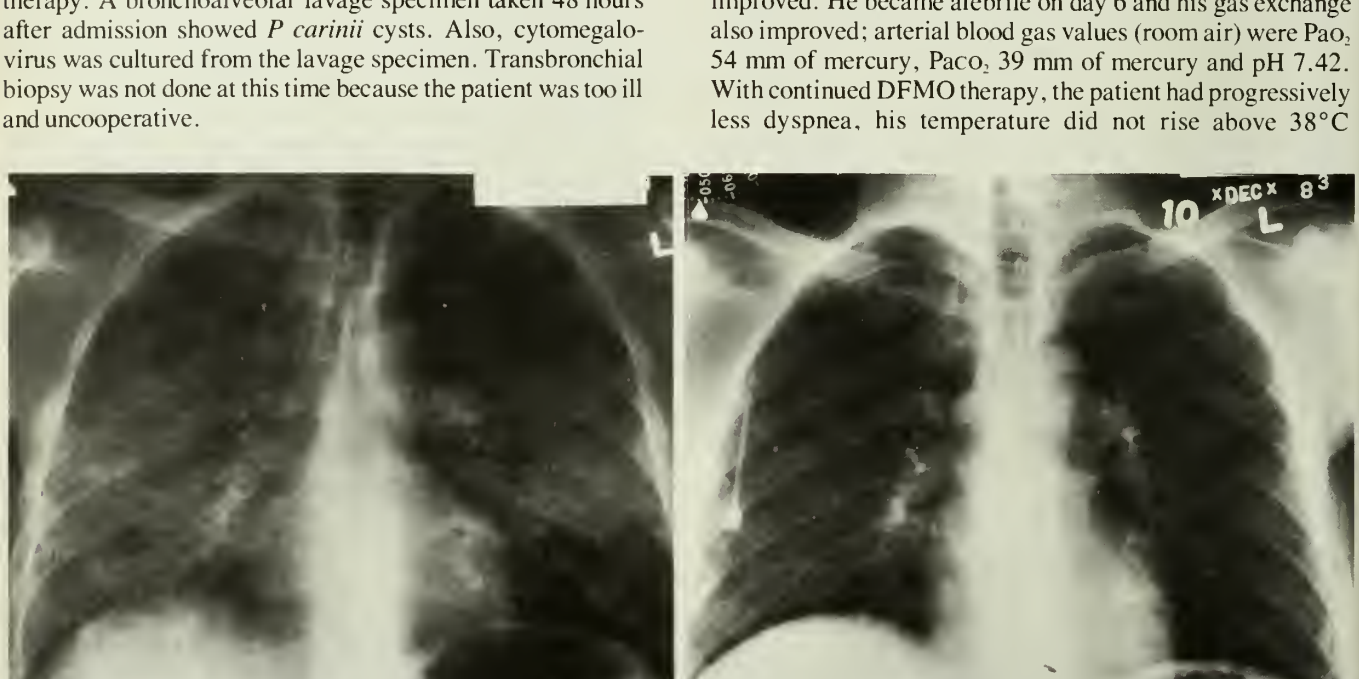

Figure 3.—Chest roentgenograms in patient 2, before **(left)** DFMO therapy showing diffuse infiltrates and after **(right)** eight weeks of DFMO therapy showing near complete resolution of infiltrates.

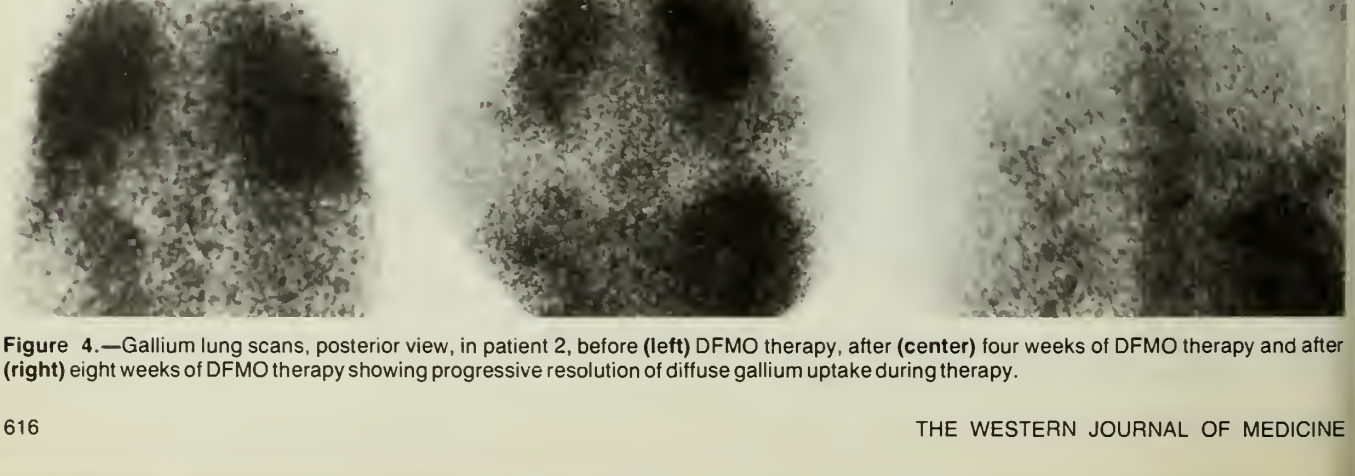

Figure 4.—Gallium lung scans, posterior view, in patient 2, before **(left)** DFMO therapy, after **(center)** four weeks of DFMO therapy and after **(right)** eight weeks of DFMO therapy showing progressive resolution of diffuse gallium uptake during therapy.

(100.4°F) and findings on roentgenograms of the chest slowly improved. However, pancytopenia developed slowly during the course of DFMO therapy. Before this therapy, the complete blood count included hemoglobin, 10.4 grams per dl; hematocrit, 30%; leukocyte count, 5,100 per μl, and platelet count, 302,000 per μl. After 27 days of therapy, the values were hemoglobin, 8.3 grams per dl; hematocrit, 25%; leukocyte count, 3,100 per μl, and platelet count, 54,000 per μl. At this time, we discontinued DFMO administration. Four days later, the leukocyte count had fallen to 1,400 per μl and the platelet count had fallen to 27,600 per μl. A bone marrow biopsy at that time showed erythroid hypoplasia, normal megakaryocytes and some myeloid immaturity. There was no circulating antiplatelet antibody.

At this time, arterial blood gases (room air) were Pao_2 72 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.46. A chest roentgenogram showed resolution of the prior diffuse infiltrates, with infiltrates persisting only in the upper lung fields bilaterally. A gallium lung scan showed resolution to grade 1 in the lower lung fields and grade 3 uptake in both upper lung fields (Figure 4). A bronchoalveolar lavage specimen showed *P carinii* cysts; a transbronchial biopsy showed persistent *P carinii* pneumonia. The patient's immunologic state showed no change at this time. Before DFMO therapy, the patient had 12% helper T cells (normal, 39% to 53%), 42% suppressor T cells (normal, 18% to 27%) and a helper:suppressor ratio of 0.3 (normal, 1.8 to 2.4); these values did not change following DFMO therapy.

The patient's hematologic state improved one week after DFMO therapy was discontinued; the leukocyte count was 3,300 per μl and the platelet count was 330,000 per μl. DFMO therapy was reinstituted at 4 grams per sq m per day by oral administration, and continued at this dosage until the eight-week course was completed. At this time, findings on a chest roentgenogram were nearly normal (Figure 3). A gallium lung scan (Figure 4) showed dramatic improvement with focal grade 2 uptake localized to the middle of the right lung. Arterial blood gas values (room air) were Pao_2 70 mm of mercury, $Paco_2$ 33 mm of mercury and pH 7.44. No cysts of *P carinii* were found in the bronchoalveolar lavage specimen and only scattered cysts were found in the transbronchial biopsy specimen. Cytomegalovirus was cultured from the bronchoalveolar lavage specimen.

The patient was discharged from hospital and did well for three months. However, he was readmitted March 30, 1984, with a one-week history of dyspnea and severe diarrhea associated with a 9-kg (20-lb) weight loss. On physical examination he was cachectic-appearing with 32 respirations per minute, oral mucosal candidiasis and funduscopic findings consistent with cytomegalovirus retinitis. A roentgenogram of the chest showed diffuse infiltrates; arterial blood gas values (room air) were Pao_2 59 mm of mercury, $Paco_2$ 31 mm of mercury and pH 7.47. *P carinii* pneumonia was diagnosed by transbronchial biopsy. After 11 days of pentamidine therapy the patient was more dyspneic; arterial blood gas values (room air) were Pao_2 33 mm of mercury, $Paco_2$ 38 mm of mercury and pH 7.50; the chest roentgenogram showed increased infiltration and the gallium lung scan showed diffuse grade 4 uptake. He was again considered unresponsive to pentamidine therapy and it was discontinued. On April 10, 1984, therapy with DFMO was begun at 6 grams per sq m per day in three divided doses given intravenously. After 11 days of DFMO administration the patient was less dyspneic and a roentgenogram of the chest showed decreased infiltration, which progressively cleared on subsequent studies. Gallium lung scans after 35 and 56 days of DFMO therapy showed dramatic progressive improvement; the latter study showed only focal grade 2 uptake. On repeat bronchoscopy after eight weeks of DFMO therapy the transbronchial biopsy specimen was negative for *P carinii* pneumonia and no cysts were found on bronchoalveolar lavage. The patient was discharged on June 13, 1984, with hyperalimentation for progressive weight loss associated with massive diarrhea that defied diagnosis. He died at home one month later.

Patient 3

A 40-year-old white homosexual man was admitted to hospital on September 23, 1983, after three weeks of progressive dyspnea on exertion and nonproductive cough, diarrhea and weight loss. During the four months before admission, he had complained of malaise and fever and had been found to have oral mucosal candidiasis, hepatosplenomegaly and a positive urine culture for cytomegalovirus.

On physical examination the patient was notably thin; his temperature was 38.5°C and he was breathing 20 times per minute. He had oral mucosal candidiasis and bilateral rales were noted on chest auscultation. Arterial blood gas values (room air) were Pao_2, 79 mm of mercury; $Paco_2$, 37 mm of mercury and pH 7.45. A roentgenogram of the chest showed bilateral infiltrates, predominantly in the upper lobes. A transbronchial biopsy of the left upper lobe revealed *P carinii* pneumonia.

TMP-SMX therapy was begun on September 24. Seventeen days later, because of worsening findings on chest roentgenograms and persistent temperature elevations to 40°C, TMP-SMX was replaced by pentamidine therapy. A gallium lung scan showed diffuse grade 3 gallium uptake. The pentamidine caused side effects including pain at the injection site and hypotension. Because of the side effects, further elevation of temperature and progressive infiltrates on the chest roentgenogram, pentamidine was discontinued after two weeks. At this time the patient had fever and dyspnea on exertion, although arterial blood gases (room air) were Pao_2 100 mm of mercury, $Paco_2$ 36 mm of mercury and pH 7.48. A bronchoscopic examination was done on November 3. Transbronchial biopsy of the left upper lobe showed *P carinii* pneumonia, and the bronchoalveolar lavage specimen grew cytomegalovirus and a few colonies of cryptococci. On the day of bronchoscopy, blood cultures were positive for cryptococci. On November 5, amphotericin B therapy was initiated. DFMO therapy was begun at the same time because of temperature elevation, worsening findings on chest roentgenograms and bronchoscopic evidence of persistent *P carinii* pneumonia. At this time the hemoglobin was 10.8 grams per dl, the hematocrit, 32%; the leukocyte count, 1,300 per μl, and the platelet count, 94,000 per μl. Enumeration of T-cell subsets was not done. A gallium lung scan showed diffuse grade 3 gallium uptake unchanged from the earlier study done after 17 days of TMP-SMX therapy.

Before the initiation of DFMO and amphotericin B therapy, the patient had been persistently febrile with temperatures ranging from 38.5°C to 40°C. By the fifth day of

therapy, he felt better and was afebrile. He remained essentially afebrile for the next six weeks, after which he was discharged from hospital. It should be noted that when he became afebrile, he had received a total dose of amphotericin B of only 60 mg because of renal toxicity; during his entire hospital stay, he received only 15 mg of amphotericin B every other day, for a total dose of 340 mg. A roentgenogram of the chest taken on the eighth day of DFMO and amphotericin B therapy showed improvement. On the tenth day, however, the patient's platelet count began to fall, although the leukocyte count remained above 1,000 per μl and the hemoglobin remained at 10 grams per dl, with a hematocrit of 30%. By the 24th day of therapy, the platelet count was 35,000 per μl and the leukocyte count had fallen to 900 per μl. DFMO therapy was discontinued. One week later, the platelet count had risen to 90,000 per μl and the leukocyte count to 1,500 per μl. DFMO therapy was restarted at 4 grams per sq m per day.

Evaluation after four weeks of orally administered DFMO (24 days at 6 grams per sq m and 5 days at 4 grams per sq m) showed continued improvement in the findings on chest roentgenograms; the last film taken in hospital on December 10 was almost normal. A gallium scan on December 9 showed improvement compared with the baseline scan of November 7, 1983, with only a trace of focal grade 2 gallium uptake at the left base of the lung and no abnormalities in the right lung. Bronchoscopy on December 12 showed only a few cysts of *P carinii* in the bronchoalveolar lavage specimen. The transbronchial biopsy was negative for *P carinii* pneumonia. Viral cultures of bronchoscopically derived lung lavage and tissue were negative for cytomegalovirus. While the patient was an outpatient, the platelet count again started to fall. On December 24, with a platelet count of 50,000 per μl, DFMO therapy was again discontinued with subsequent elevation of the platelet count. Although the patient's clinical condition as an outpatient improved initially, elevated temperatures associated with progressively severe inanition subsequently developed and he died on February 6, 1984. The lung parenchyma at autopsy was hemorrhagic with intranuclear inclusions within enlarged alveolar lining cells typical of cytomegalovirus. There was no evidence of *P carinii* pneumonia or cysts. Inclusions typical of cytomegalovirus were identified in other organs: small and large intestines, liver, pancreas, thyroid, adrenals (associated with hemorrhagic necrosis) and kidney. The autopsy diagnosis was disseminated cytomegalovirus infection.

Patient 4

A 36-year-old white homosexual man with Kaposi's sarcoma was admitted to hospital on October 24, 1983, after three weeks of fever, progressive shortness of breath and nonproductive cough. Seven months earlier, he had lost 9 kg (20 lb) and suffered shortness of breath; *P carinii* pneumonia had been diagnosed by bronchoscopy. He had initially been treated with TMP-SMX but, after five days, with worsening arterial blood gas values and chest roentgenographic findings, the therapy was changed to pentamidine, to which he responded.

On physical examination on admission the patient was noted to be in moderate respiratory distress, breathing 30 times per minute, with a nonproductive cough, a temperature of 40.5°C (105°F) and oral mucosal candidiasis. Skin examination showed diffuse Kaposi's sarcoma. The arterial blood gas values (room air) were Pao_2 85 mm of mercury, $Paco_2$ 21 mm of mercury and pH 7.51. The chest roentgenogram showed diffuse interstitial infiltrates, with a dense consolidation in the upper lobe of the right lung.

On October 28, after *P carinii* pneumonia had been diagnosed by transbronchial biopsy, pentamidine therapy was begun. In addition, the bronchoalveolar lavage specimen grew cytomegalovirus. Because blood cultures were positive for *Streptococcus pneumoniae,* penicillin therapy was also initiated. The patient remained febrile, and after five days of therapy, on November 2, a diffuse erythematous skin eruption appeared, requiring that both pentamidine and penicillin administration be discontinued. The chest roentgenogram was unchanged. Arterial blood gas values (room air) were Pao_2 84 mm of mercury, $Paco_2$ 22 mm of mercury and pH 7.48. Erythromycin therapy was initiated for the streptococcal infection, but the *P carinii* pneumonia was not treated for three days. During that time the patient's cough worsened and his temperature was between 38°C and 39°C. On November 5, DFMO therapy was begun. At this time, arterial blood gas values (room air) were Pao_2 77 mm of mercury, $Paco_2$ 24 mm of mercury and pH 7.49. A gallium lung scan was not done at this time. Subset enumeration of T cells was not carried out in this patient.

After two days of DFMO therapy, the patient felt better and became afebrile. Arterial blood gas values (room air) were Pao_2 90 mm of mercury, $Paco_2$ 30 mm of mercury and pH 7.43. By day 6 of therapy the leukocyte count had decreased from 6,600 per μl at the initiation of DFMO therapy to 2,200 per μl. The patient was discharged on November 11 on a regimen of the same oral dosage of DFMO. In follow-up as an outpatient, after ten days of DFMO therapy, his leukocyte count had further decreased to 1,900 per μl. He was feeling well and arterial blood gas values were Pao_2 99 mm of mercury, $Paco_2$ 32 mm of mercury and pH 7.44. Because of the falling leukocyte count, however, DFMO administration was discontinued after 13 days of therapy. Three days later, the leukocyte count was 2,200 per μl and DFMO therapy was restarted at a lower oral dosage (4 grams per sq m per day). It was continued at this dose, with the patient's leukocyte counts ranging between 2,000 and 2,400 per μl until the eight-week course was completed. At that time, the patient had no cough and only minimal dyspnea on exertion. He was afebrile. The leukocyte count was 2,400 per μl, platelet count 235,000 per μl and the hemoglobin 10 grams per dl; the hematocrit was 29%. Arterial blood gases (room air) were Pao_2 96 mm of mercury, $Paco_2$ 30 mm of mercury and pH 7.45. Roentgenograms of the chest showed improvement but minimally increased interstitial markings were noted. A gallium lung scan showed diffuse grade 1 uptake. Bronchoscopy showed multiple dark airway lesions consistent with Kaposi's sarcoma. The transbronchial biopsy was negative for *P carinii* pneumonia but a few cysts were evident on the bronchoalveolar lavage specimen. Cytomegalovirus was cultured from this lavage specimen. The patient did well for two months after DFMO therapy at which time elevated temperatures developed associated with severe inanition and he died. He had requested no specific or supportive therapy. An autopsy was not carried out.

Patient 5

A 45-year-old white homosexual man was admitted to hospital on March 27, 1984, after one week of dyspnea. Two years before admission he had atypical pneumonia and was treated with TMP-SMX to which a severe cutaneous reaction developed. Physical examination on admission showed diffuse adenopathy and oral mucosal candidiasis. Chest roentgenograms showed bilateral infiltrates; arterial blood gas values (room air) were Pao_2 56 mm of mercury, $Paco_2$ 30 mm of mercury and pH 7.51. Transbronchial biopsy showed *P carinii* pneumonia. On March 28 he was given TMP-SMX, which resulted in an immediate rash after the second oral

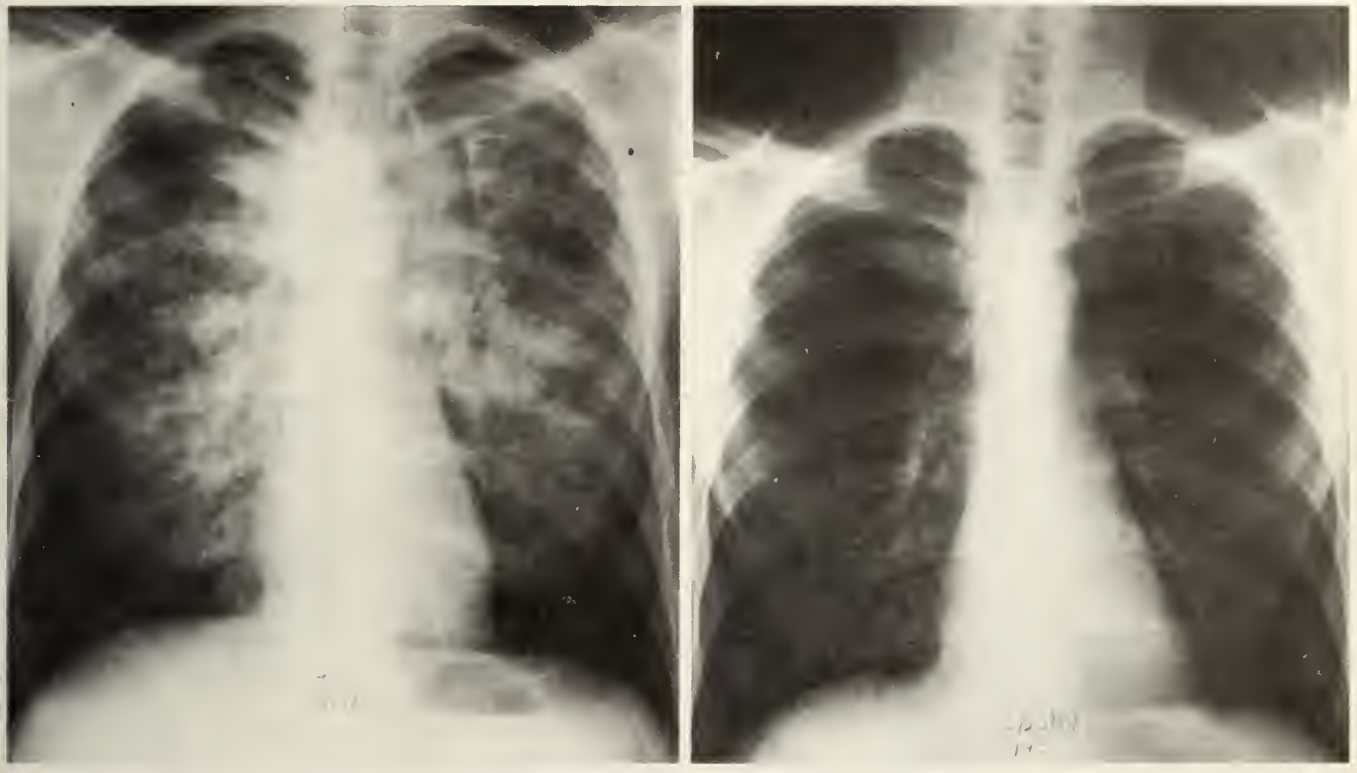

Figure 5.—Chest roentgenograms in patient 5, before **(left)** DFMO therapy for recurrent *Pneumocystis* pneumonia showing diffuse infiltrates and after **(right)** eight weeks of treatment with DFMO showing resolution of infiltrates.

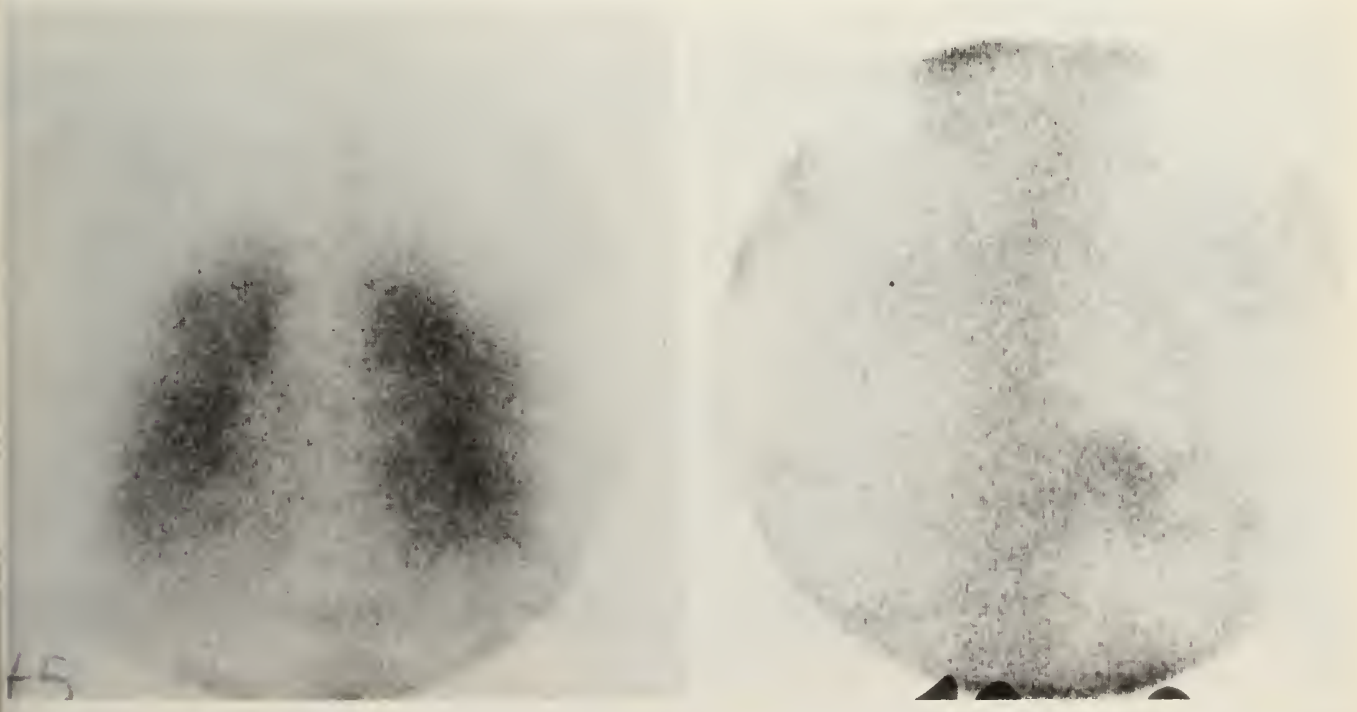

Figure 6.—Gallium lung scans, posterior view, in patient 5, before **(left)** DFMO therapy for recurrent *Pneumocystis* pneumonia showing diffuse gallium uptake and after **(right)** eight weeks of treatment with DFMO showing near complete resolution of gallium uptake.

dose; TMP-SMX therapy was discontinued and pentamidine therapy was begun. After three days of pentamidine therapy, the patient became afebrile. After five days, however, recurrent temperature elevation and rash developed, and liver function test results were abnormal. Pentamidine administration was discontinued after 14 days because of these toxicities. The patient remained in hospital for seven days with no therapy for his pneumonia. He was discharged at that time with less dyspnea, and arterial blood gas values (room air) were Pao_2 90 mm of mercury, $Paco_2$ 25 mm of mercury and pH 7.46. A roentgenogram of the chest showed improvement compared with a study done on admission.

The patient was readmitted three days later, ten days after pentamidine therapy had been discontinued, with severe dyspnea, temperature to 41°C (105.8°F), progressive infiltration on chest roentgenograms and a diffuse grade 4 gallium lung scan (Figures 5 and 6); arterial blood gas values were Pao_2 58 mm of mercury, $Paco_2$ 24 mm of mercury and pH 7.53. A repeat transbronchial biopsy showed *P carinii* pneumonia. The patient was given DFMO; pentamidine therapy was not reinstituted. After five days of DFMO therapy, he became afebrile; arterial blood gases were Pao_2 66 mm of mercury, $Paco_2$ 31 mm of mercury and pH 7.5. After ten days of DFMO therapy he was asymptomatic and was discharged from the hospital; arterial blood gas values (room air) were Pao_2 83 mm of mercury, $Paco_2$ 35 mm of mercury and pH 7.46.

The patient did well as an outpatient; he returned to work for the last six of his eight weeks of DFMO therapy. The post-DFMO repeat transbronchial biopsy showed no *P carinii* pneumonia, and bronchoalveolar lavage was negative for cysts. A gallium lung scan showed resolution with only a focal right lower lobe grade 2 uptake of gallium and a roentgenogram of the chest showed no abnormalities (Figures 5 and 6). He has continued to do well for two months after DFMO therapy was discontinued. The patient's helper-to-suppressor T-cell ratio was 0.3 (normal, 1.8 to 2.4) before DFMO therapy and did not change after eight weeks of therapy. Cultures of lung lavage and transbronchial biopsy both before and after DFMO therapy failed to grow cytomegalovirus. Finally, there were no side effects attributable to DFMO.

Patient 6

A 51-year-old white homosexual man was evaluated on July 5, 1984, for four months of daily temperature elevation to 40°C (104°F) associated with night sweats and progressive dyspnea. Physical findings included a temperature of 38.5°C and oral mucosal candidiasis. A chest roentgenogram showed bilateral interstitial infiltrates; there was grade 4 gallium uptake on a gallium lung scan (Figures 7 and 8). Arterial blood gas values (room air) were Pao_2 83 mm of mercury, $Paco_2$ 33 mm of mercury and pH 7.44. Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage showed *P carinii* pneumonia.

The patient had a history of severe cutaneous reaction to TMP-SMX and refused pentamidine therapy as well as admission to hospital. On July 7, 1984, he began DFMO therapy as an outpatient. After two days, he became and remained afebrile. After five days he was no longer dyspneic, and arterial blood gases (room air) were Pao_2 94 mm of mercury, $Paco_2$ 36 mm of mercury and pH 7.43; a chest roentgenogram showed significant improvement. The next chest roentgenogram done after 24 days of DFMO therapy showed no abnormalities (Figure 7). A repeat gallium lung scan at this time showed resolution to bibasilar focal grade 2 gallium uptake (Figure 8).

After six weeks of DFMO therapy the patient remained afebrile, with no dyspnea. In terms of other potential benefit from DFMO, the helper-to-suppressor T-cell ratio was 0.09 (normal, 1.8 to 2.4) before DFMO therapy and did not change after six weeks of therapy. Culture of the initial trans-

Figure 7.—Chest roentgenograms in patient 6, before **(left)** DFMO therapy showing bilateral infiltrates and after **(right)** 24 days of treatment with DFMO as first-line therapy showing a normal study.

bronchial biopsy and bronchoalveolar lavage was negative for cytomegalovirus; the patient refused a repeat bronchoscopy following DFMO therapy. The only apparent side effect was a decrease in the platelet count from 174,000 per μl before therapy to 83,000 per μl after five weeks of DFMO therapy. After another week of therapy, the platelet count spontaneously increased to 130,000 per μl.

Discussion

P carinii pneumonia, if untreated, is fatal in 90% to 100% of patients.[35] Pentamidine was the first effective drug to treat *P carinii* pneumonia, but it causes significant adverse effects in almost half of the patients.[11,12] Subsequently, TMP-SMX was used to treat this infection.[9,10] In patients who do not have AIDS, TMP-SMX is as effective as pentamidine against *P carinii* pneumonia and has few adverse effects.[13] In patients with AIDS, however, TMP-SMX has been associated with significant toxicity. Approximately half the AIDS patients given TMP-SMX for *P carinii* pneumonia have had severe drug reactions, including fever, cutaneous reactions and life-threatening cytopenia.[6-8] Clearly, a new medication is needed for *P carinii* pneumonia in patients with AIDS. The recently recognized antiprotozoan effect of DFMO made this compound a possible new treatment for *P carinii* pneumonia.[14]

Patient 1 could not tolerate TMP-SMX. After eight days of pentamidine therapy, he had increased dyspnea and temperature elevation, and more infiltration shown on chest roentgenograms, as well as increased hypoxia. A gallium lung scan showed diffuse grade 3 gallium uptake, and bronchoscopy showed persistent *P carinii* pneumonia. After four days of DFMO therapy, the patient's temperature was normal; after one week of therapy, the chest roentgenogram showed improvement and arterial blood gas values were normal. After 30 days of DFMO therapy, the gallium lung scan was normal, transbronchial biopsy failed to show *P carinii* pneumonia and bronchoalveolar lavage showed no *P carinii* cysts.

After six days of pentamidine therapy, patient 2 remained in a toxic-appearing condition, with elevated temperature, worsened findings on roentgenograms of the chest and arterial blood gas studies and diffuse grade 4 gallium uptake on a gallium lung scan. After six days of DFMO therapy, he became afebrile and the arterial blood gas values and chest roentgenogram were improved. In addition, serial gallium scans of the lung showed progressive improvement concomitant with improved serial chest roentgenographic findings and arterial blood gas analyses. Bronchoscopy after eight weeks of DFMO therapy showed only scattered cysts of *P carinii* on the transbronchial biopsy and no cysts in the bronchoalveolar lavage specimen. The patient did well for three months before recurrent *P carinii* pneumonia developed, which again was refractory to pentamidine therapy. Although the patient's course was complicated by severe diarrhea, he again responded to eight weeks of DFMO therapy. After this second course of DFMO repeat transbronchial biopsy and bronchoalveolar lavage were negative for both *P carinii* pneumonia and cysts.

Patient 3 had persistent *P carinii* pneumonia despite 17 days of TMP-SMX and two weeks of pentamidine therapy. He also had cryptococcal organisms in the bronchoalveolar lavage specimen and cryptococcemia. The simultaneous initiation of amphotericin B and DFMO complicates interpretation of the benefit of DFMO in this patient. However, the patient became afebrile on the fifth day of therapy, when he had received a total dose of only 60 mg of amphotericin B. The rapid clinical response more likely reflects effective treat-

Figure 8.—Gallium lung scans, posterior view, in patient 6, before **(left)** DFMO therapy showing diffuse grade 4 gallium uptake and after **(right)** 24 days of treatment with DFMO as first-line therapy showing resolution to bibasilar focal grade 2 gallium uptake.

ment of *P carinii* pneumonia with DFMO than a response of pulmonary cryptococcosis to 60 mg of amphotericin B. After five weeks of DFMO and amphotericin therapy, the patient remained afebrile and felt well, and the abnormalities on chest roentgenograms and gallium lung scans had resolved. Finally, bronchoscopy near the completion of DFMO therapy showed no *P carinii* pneumonia on transbronchial biopsy and only a few cysts in the bronchoalveolar lavage specimen. The patient subsequently died of disseminated cytomegalovirus infection. At autopsy, six weeks after DFMO therapy was discontinued, neither *P carinii* pneumonia nor cysts were identified in the lung pathologic findings.

Interpreting the benefit of DFMO in patient 4 is complicated by concurrent treatment with erythromycin for *Streptococcus pneumoniae*. After discontinuing pentamidine administration, and while taking erythromycin but no therapy for *P carinii* pneumonia, the patient's clinical condition deteriorated. After two days of treatment with DFMO, he became afebrile and subsequent arterial blood gas analyses and chest roentgenograms showed improvement. There was no gallium uptake in his lungs (grade 1) after eight weeks of DFMO therapy. He remained well for an additional two months following cessation of DFMO therapy. Subsequently an acute undiagnosed illness developed and the patient died; no autopsy was carried out. The role of effective antibacterial therapy for *S pneumoniae* infection cannot be discounted in his initial clinical improvement. However, the sustained clinical improvement for four months after the diagnosis of *P carinii* pneumonia implies likely benefit from DFMO.

Although DFMO appeared to be beneficial in treating *P carinii* pneumonia in patients 1 through 4, who were failing or intolerant to conventional therapy, these cases are somewhat difficult to interpret because of the prior use of TMP-SMX or pentamidine, or both. The presence of other treatable infections in patients 3 and 4 further complicates the interpretation. First-line and near-first-line use of DFMO in patients 5 and 6, however, provides a more cogent argument for the effectiveness of DFMO therapy. In addition, cases 5 and 6 were not complicated by other infections. Patient 5 was responding to pentamidine therapy when it was stopped after 14 days because of liver toxicity. Over the next ten days without therapy for *P carinii* pneumonia the patient relapsed, with recurrent dyspnea, fever, hypoxia and progressive infiltration on chest roentgenograms. Rather than reinstituting pentamidine therapy, we treated the patient with DFMO; he responded quickly, was discharged after ten days of DFMO administration and returned to work. Finally, the efficacy of DFMO is established most clearly in case 6. This patient was put directly on a regimen of DFMO alone without previous conventional therapy. He never required admission to hospital and had an unequivocally positive response to DFMO therapy for *P carinii* pneumonia.

In the six patients studied, clinical evaluation—including dyspnea and temperature, as well as the findings on chest roentgenograms, arterial blood gas studies and gallium lung scans—clearly implies that DFMO was beneficial. After DFMO therapy, patients 2, 3 and 4 still had *P carinii* cysts in their lungs despite resolution of *P carinii* pneumonia. The persistence of *P carinii* cysts on bronchoscopic evaluation with clinical and objective resolution of the pneumonia seems unique to AIDS patients, independent of the drug used for therapy. Such persistence is not seen in patients without AIDS, and its significance is unclear.[11,36]

The potential effects of DFMO on cytomegalovirus and helper and suppressor T-cell populations suggest that, in addition to its usefulness as an antiprotozoan agent, DFMO might have other benefits for patients with AIDS.[24,26] In this preliminary report, DFMO apparently did not affect either cytomegalovirus or immune incompetence. Patients 2 and 4 had cytomegalovirus cultured from the lung before and after DFMO therapy. Although patient 3 did not have cytomegalovirus on his post-DFMO therapy bronchoscopic evaluation, an autopsy six weeks after DFMO was discontinued showed he died of disseminated cytomegalovirus infection. Patients 1, 5 and 6 never had a diagnosis of pulmonary cytomegalovirus infection. Similarly, in four patients (patients 1, 2, 5 and 6) DFMO did not affect T-cell subset populations.

Previous experience has suggested that DFMO may cause reversible hearing defect, gastrointestinal disturbances or reversible hematologic abnormalities.[37] None of our six patients complained of hearing problems or had objective hearing defects ascribable to DFMO. No patient complained of gastrointestinal side effects referrable to DFMO. However, hematologic side effects did occur. Patient 1 incurred a low-grade neutropenia that did not require discontinuing the therapy. His persistently low leukocyte count five months after the cessation of DFMO is consistent with AIDS and was not necessarily a drug reaction. Patient 2 had pancytopenia that eventually required stopping DFMO therapy. The severe thrombocytopenia and neutropenia were reversed after one week, and hematologic toxicity did not recur when DFMO was reinstituted at a lower dose. Patient 3 had two reversible episodes of thrombocytopenia. Patient 4 had a reversible decrease in his leukocyte count, which did not recur when DFMO was reinstituted at a lower dose. Patient 6 had a decrease in platelet count, which spontaneously resolved with no change in DFMO therapy.

Conclusion

Although encouraging, our preliminary experience with DFMO therapy for *P carinii* pneumonia among patients with AIDS is insufficient to permit an overall comparison of DFMO efficacy with that of TMP-SMX and pentamidine. However, these six AIDS patients, all unresponsive or intolerant of conventional therapy for *P carinii* pneumonia, benefited from treatment with DFMO. If results in such patients continue to be favorable, future studies should include a comparison of DFMO and conventional therapy.

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Clinical Medicine

Evaluation of Hemoptysis in Patients With a Normal Chest Roentgenogram

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Hemoptysis is a common presenting complaint in patients with pulmonary disease. Although controversial, many clinicians suggest that all patients with hemoptysis should be evaluated with bronchoscopy to exclude the presence of a serious pathologic condition. We reviewed records for an 18-month period, during which 113 patients had hemoptysis as their principal complaint. In all, 26 of the 113 patients had normal chest roentgenograms. All underwent bronchoscopy as part of their evaluations. Results of bronchoscopy in these patients neither altered therapeutic decisions nor led to diagnoses of specific pathologic processes. We conclude that close observation of patients with normal chest roentgenograms who have hemoptysis may be an acceptable clinical approach.

(Peters J, McClung HC, Teague RB: Evaluation of hemoptysis in patients with a normal chest roentgenogram. West J Med 1984 Nov; 141:624-626)

Hemoptysis accounts for about 10% to 15% of all pulmonary consultations.[1,2] The symptom itself is of little diagnostic use because it is nonspecific; in fact, it has been associated with more than 100 causes.[1] Furthermore, it is not a sensitive indicator since the quantity and duration of hemoptysis correlate neither with the clinical outcome nor with the seriousness of the cause.[3,4] Dogma in much of the pulmonary literature and in many teaching institutions dictates that all patients who have blood in the sputum should undergo a full-scale evaluation including bronchoscopy, even though 25% to 30% of these patients have normal roentgenograms.[5-8] The justification for this approach has usually been to search for a radiographically occult neoplasm and to identify a site of bleeding in order to guide possible surgical interventions.[5,6] Therefore, to assess the utility of this approach in our patients with hemoptysis, we reviewed the results of this procedure specifically to determine if it aided in the management either diagnostically or therapeutically of patients with normal chest roentgenograms.

Methods

We reviewed the records of 113 patients who were admitted with hemoptysis from July 1979 to January 1981. All patients underwent fiberoptic bronchoscopy by the transnasal approach using topical anesthesia provided by 1% lidocaine. The procedure was done either by pulmonary fellows under supervision or by faculty instructors. All procedures used the Olympus model BF-B2 or B3 fiberoptic bronchoscope (Olympus Corporation of America, New Hyde Park, New York).

Bronchial and transbronchial biopsies as well as brushings were done under fluoroscopic guidance when indicated. The bronchoscope was retroflexed to visualize the posterior nasopharynx in cases where upper respiratory tract bleeding was a possibility. All areas that were actively bleeding and all suspicious areas were brushed and routinely lavaged with nonbacteriostatic saline solution for cytologic evaluation. Whether or not tissue samples were cultured for acid-fast bacillus and fungus was dictated by the clinical signs. Investigation of the airways lasted 30 to 45 minutes. The procedure and its findings were recorded in the patient's chart at the time of bronchoscopy. Medical records were analyzed for previous episodes of hemoptysis, duration of hemoptysis, quantity of sputum and change in therapeutic approach based on bronchoscopic examination. Also, initial postero-anterior and lateral roentgenograms were considered normal when the radiologist and the pulmonary consultant independently agreed before the bronchoscopy that the roentgenogram was within normal limits. For the purpose of this study, roentgenographic evidence of emphysema was not considered a specific abnormality, but all other findings including suspicious hilar structure or scarring seen on any portion of the roentgenogram were considered grounds to classify the roentgenogram as abnormal.

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Results

For the purpose of comparison, the patients were divided into four groups on the basis of their final diagnosis: neoplasm, tuberculosis, miscellaneous (bronchiectasis, pneumonia, abscess and the like) and undiagnosed. "Bronchitis" was excluded as a definitive diagnosis for hemoptysis. It is a clinical diagnosis or one inferred from visual inspection of the bronchial tree, and we found that an equal number of patients whose condition had an identified cause as those who had none had a diagnosis of "bronchitis." Two groups were compared: those with normal roentgenograms and those with abnormal roentgenograms. The two groups were comparable in mean age (52 years versus 53 years), smoking history (40 pack-years for both groups) and frequency of identifying the bleeding site (40% versus 34%). Of 113 patients, 26 with hemoptysis had normal roentgenograms. In 10 of these 26 patients, the bleeding site could be localized. The ability to identify a site of bleeding roughly correlated with the rate of bleeding (Table 1). In both patients with massive hemoptysis (more than 600 ml in 24 hours), the site of bleeding could be localized, whereas in only 8 of 24 patients with milder hemoptysis could the site of bleeding be identified. In the two patients with massive hemoptysis, the localization of the bleeding site would have been important had the bleeding not stopped spontaneously. Identification of the bleeding site, however, did not change the therapeutic approach in any of the 26 patients, because none required surgical treatment. Perhaps more importantly, no pulmonary pathologic diagnosis was made in any of these 26 patients. Two patients were found to have nasopharyngeal bleeding sites that were easily controlled. No patient with hemoptysis who had a normal chest roentgenogram died during hospitalization and none required surgical intervention. Unfortunately, only 9 of 26 patients were effectively followed after discharge for an average of 4.5 months (range 1 to 12 months). These patients were comparable in mean age (51 years old) and smoking history (39 pack-years) to those patients lost to follow-up. Only one patient continued to have hemoptysis. For reasons not yet determined, this patient has had blood streaking in the sputum for more than one year and has not developed any abnormality of the roentgenogram.

By comparison, the group with abnormal chest roentgenograms (87 of 113) was not significantly different from groups described in the literature.[9-11] Again, the ability to identify the site of bleeding was roughly correlated with the briskness of bleeding at the time of bronchoscopy. The fact of identification again did not aid in the initial therapy, because none of the patients required immediate surgical intervention. A cause for the hemoptysis in this group was determined in 33 of 87 patients. Nineteen had neoplasm, seven had tuberculosis and seven had a miscellaneous group of pulmonary pathologic conditions (Table 1).

Discussion

Hemoptysis is a common symptom of patients who visit lung specialists. Pulmonologists and other clinicians must then decide how extensively they should seek a cause for this symptom. Many of these patients have no radiographic evidence of a significant thoracic disease process, yet much of the literature suggests that all patients with hemoptysis should undergo bronchoscopic evaluation. In an attempt to better select patients for bronchoscopy, Weaver and co-workers suggested that only patients who were over 40 years old, were smokers or whose hemoptysis had lasted more than one week should be subjected to this procedure.[12]

Many physicians disagree with this viewpoint, feeling that if hemoptysis occurs, a cause for it should be found.[8,13] Further, some authors have emphasized that carcinoma may be heralded by hemoptysis even if no radiographic abnormalities are present.[5,6] Although this undoubtedly occurs, our experience suggests that it is an uncommon sign of bronchogenic carcinoma; more commonly, hemoptysis occurs later in the course of the disease, at which point it can be related to sloughing attendant to advanced tumor growth. Our experience with a group of patients who are very predisposed to the development of bronchogenic carcinoma has shown that bronchoscopy adds nothing either diagnostically or therapeutically to management of the disease.

Some of the confusion about whether or not hemoptysis is a sign of carcinoma when the roentgenogram is normal may be related to the criteria for a "negative" chest roentgenogram. Kallenbach[6] defined a normal roentgenogram as one without a

TABLE 1.—*Correlation of Radiologic Findings and Hemoptysis in 113 Patients*

Type of Chest Roentgenogram	*Number of Patients*	*Site of Bleeding Identified*	*Pulmonary Pathology Identified*	*Change in Therapeutic Program (Surgery, Radiation, Antibiotics)*
Normal Roentgenograms				
Minimal hemoptysis (< 50 ml/24 hr)	10	1 (10%)	0*	1
Moderate hemoptysis (50-600 ml/24 hr)	14	7 (50%)	0	0
Massive hemoptysis (> 600 ml/24 hr)	2	2 (100%)	0	0 †
All normal roentgenograms	26	10	0	0
Abnormal Roentgenograms				
Minimal hemoptysis	41	8 (20%)	12 (29%)	11 (26%)
Moderate hemoptysis	32	9 (29%)	13 (39%)	13 (39%)
Massive hemoptysis	14	7 (50%)	8 (58%)	7 (50%)
All abnormal roentgenograms	87	24	33 (38%)‡	31 (28%)
All patients	113	34 (30%)	33 (29%)	32 (28%)

* Two patients found to have nasopharyngeal bleeding source; subsequently identified by ear, nose and throat examination.

† Nasopharyngeal bleeding cauterized.

‡ Neoplasm 19; tuberculosis 7, miscellaneous 7 (3 pneumonia, 2 bronchiectasis, 1 Wegner's granulomatosis, 1 fungal infection).

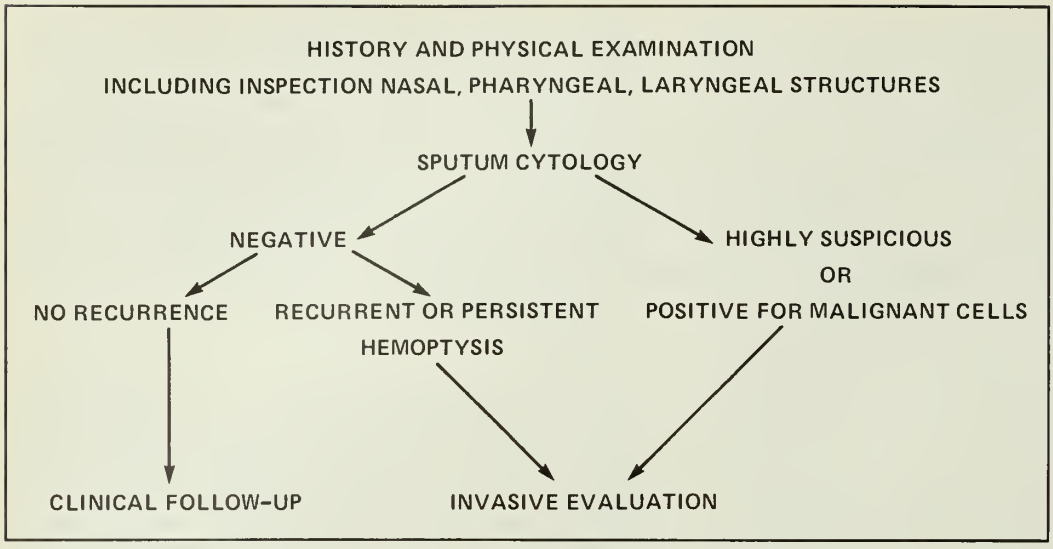

Figure 1.—Management of patients with submassive hemoptysis and normal chest roentgenograms.

mass, obstructive pneumonitis, atelectasis or effusion. Although 6 of 32 patients in this study were found to have carcinoma of the lung, there is no way to assess whether these roentgenograms were actually "normal," because enlarged pulmonary arteries, pleural thickening, granulomatous lesions and localized fibrotic changes were not reasons for exclusion from the study. All six of the patients with carcinoma of the lung that Kallenbach described as having "no radiologic evidence of tumor" were patients with recurrent hemoptysis. These data support the concept that for these patients with a normal roentgenogram, only those with suspicious or positive cytologic findings or those with recurrent hemoptysis require bronchoscopic evaluation.

Bronchoscopy is a relatively safe procedure but it carries some risk. In a survey of 48,000 procedures there were 12 deaths and a number of life-threatening complications, including 27 cardiovascular complications, 52 airway complications and 41 reactions to anesthesia.[14] Equally relevant is the patient time and expense the procedure entails. Therefore, it would appear from our data that a reasonable alternative approach for management of patients with hemoptysis and a normal chest radiograph would be a conservative outpatient evaluation as outlined in Figure 1. A physician should visually inspect the nasal, pharyngeal and laryngeal structures as part of the physical examination in patients with hemoptysis. Cytologic screening of sputum should reveal any radiographically occult centrally located carcinomas.

A more aggressive hospital evaluation might be reserved for patients who continue to have hemoptysis, have recurrent episodes of hemoptysis, have suspicious or positive sputum cytologic findings or have massive or life-threatening degrees of hemorrhage.

Whether this more conservative approach to the management of patients with normal chest roentgenograms is valid and should be recommended awaits a prospective study with an improved long-term follow-up design. Until that time, each patient's care should be individualized. Consideration of risk factors such as age and smoking history would help determine the extent of evaluation and the duration of follow-up.

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Hepatitis B Prevention in Small Rural Hospitals

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A retrospective study of 246 potential hepatitis B exposure incidents in 12 rural hospitals in Arizona over a two-year period revealed a rate of 6.3 incidents per 100 employees per year. Needle punctures accounted for 68% of the incidents; 17% were cuts from instruments or broken glassware. Although 51% occurred in nursing personnel, housekeepers accounted for a surprising 19.5% of the reports. Only 50% of the employees received any medical attention following incidents. None received hepatitis B immune globulin (HBIG); seven received immune globulin (IG). The mean cost to the hospitals for the 122 incidents where treatment was given was $64.50 per incident. In all, 10 hospitals had no written policy for hepatitis B prevention, 3 did not stock IG and 11 did not stock HBIG. There was little awareness of hepatitis B as a nosocomial problem within these institutions, perhaps because no reported cases of clinical hepatitis B occurred in employees of the 12 hospitals in the two years.

(Dandoy S, Kirkman-Liff B: Hepatitis B prevention in small rural hospitals. West J Med 1984 Nov; 141:627-630)

Although numerous studies have focused on the risk of hepatitis B to employees of urban hospitals,[1-5] the extent of hepatitis B exposure in nonmetropolitan facilities has not been defined. Hospitals in small towns may serve populations at lower risk of carrying hepatitis B antigen and may not offer specialized services that are known to increase employee contact with blood. With the development of a vaccine for active immunization against hepatitis B,[6] medical staffs and administrators in such hospitals have been faced with deciding whether or not to use this vaccine without having data on what the actual risks may be in their facilities or what they are spending currently to prevent hepatitis B. This paper presents an analysis of the potential hepatitis B problem in 12 rural hospitals in Arizona.

Methods

There are 40 licensed general hospitals located outside the Phoenix and Tucson metropolitan areas in Arizona. Eight facilities are operated by the Indian Health Service on or near Indian reservations and two others are also federally operated (one military and one Veterans Administration hospital). Of the 30 nonfederal hospitals, 27 have fewer than 100 beds; these were chosen as the focus for this study. A 50% random sample of these small hospitals was selected. After one hospital declined to participate because of inadequate records, the sample included 12 hospitals: 7 with 50 to 100 beds and 5 with fewer than 50 beds. Each hospital was located in a different town in the state and was the only source of inpatient care in its community. The closest distance between hospitals was 25 miles; one facility was 70 miles from any other hospital. The 12 hospitals ranged in size from 23 to 92 beds and employed from 60 to 273 persons, for a total of 1,966 employees for all 12 institutions.

Each hospital was visited by project staff to obtain information on reported potential hepatitis B exposure incidents during 1980 and 1981. The definition of an exposure included any reported employee incident resulting in direct or indirect percutaneous or mucosal surface exposure to a patient's blood, serum or secretions. Information was recorded about the employee, the incident, any resulting testing or treatment and the outcome. The needed information was abstracted from employee incident or accident records, emergency room reports, personnel records and logs of occupational injuries and illnesses. Although a variety of records was used, data obtained from each hospital were comparable.

The 12 hospitals were asked to supply information on current procedures for preventing hepatitis B among employees. Also collected were data on the availability of and charges for laboratory tests and immune globulins, the charges for emergency room care and salary ranges for specific employee groups.

For each procedure, test and treatment following an inci-

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dent, billed charges were used to represent the cost of the incident. Charges associated with visits to the emergency room or a physician's office were assigned as additional costs of treatment. First aid, any treatment given at the site of the incident, history-taking and physical examination were each assigned a cost of zero because the amounts were difficult to estimate. Any work time lost, even to receive first aid, was assigned a cost, using the average wage rate for each employee's job class multiplied by the time lost from work for the diagnostic or treatment procedures. All assigned costs were multiplied and summed by the number of times that each medical service was used by each employee to obtain the cost for each incident. These costs were then averaged across the total number of incidents.

Results

Risk

Nine of the hospitals had no known cases of hepatitis B among patients admitted in 1980 or 1981. The other three hospitals had admitted a total of six patients with hepatitis B. None of the 12 institutions knew of any employees with hepatitis B in those two years. The Arizona Department of Health Services also had received no reports of any cases of hepatitis B in hospital workers from these 12 facilities. In fact, the department had records of only three cases of hepatitis B from health care workers in rural Arizona in 1980 and 1981: one from a clinic and two from Indian Health Service hospitals.

ABBREVIATIONS USED IN TEXT

HBIG = hepatitis B immune globulin
IG = immune globulin

In general these small institutions were ill prepared to manage exposures to hepatitis B. Ten had no written policy or procedure for handling hepatitis exposures. Of the two with written procedures, only one followed the recommendations of the national Advisory Committee on Immunization Practices (ACIP).[7] Although all hospitals had designated infection control nurses, most of these nurses had other assignments and lacked professional experience with hepatitis, particularly experience in differentiating between hepatitis types A and B.

In the two-year period we found records of 246 incidents that met our criteria for potential hepatitis B exposures. The overall rate was 6.3 incidents per 100 employees per year. Needle puncture wounds accounted for 68% of the incidents. The remainder were cuts from sharp instruments or broken glassware contaminated with blood (17%), blood or secretion spills (6%) or human bites (9%). One 24-bed hospital had no reports of any exposure incidents in the two-year period.

Female employees reported 83% of the exposure incidents. The job titles of exposed employees are shown in Table 1. There was only one reported incident among physicians. Rural hospitals generally do not have salaried physicians, and no effort was made to obtain information on community physicians exposed to hepatitis while in the hospital. Housekeeping staff accounted for a relatively high proportion (19.5%) of incidents, presumably because of exposure to discarded needles and broken materials in trash receptacles or linens.

For additional analysis, job titles were combined into six groups with similar functions, similar exposure situations or both, and then compared by location of incident (Table 2). Housekeepers reported that 20% of their exposure incidents occurred in the trash area and 47% on the medical or surgical units. Two thirds (66%) of the incidents among nursing staff

TABLE 1.—*Job Titles of Employees Potentially Exposed to Hepatitis B in 12 Rural Hospitals in Arizona, 1980 and 1981*

Job Title	*Number of Incidents*	*Percent of Incidents*
Nursing		
Registered nurse	54	22.0
Licensed practical nurse	26	10.7
Nursing assistant/orderly	46	18.7
Laboratory		
Laboratory technician/phlebotomist	22	8.9
Medical technologist	13	5.3
Other Technicians		
Surgical	6	2.4
Respiratory	9	3.7
Radiology	6	2.4
EKG	2	0.8
Housekeeping		
Housekeeper	48	19.5
Central supply worker	3	1.2
Physicians	1	0.4
Support Staff		
Unit clerks	6	2.4
Others	4	1.6
ALL EMPLOYEES	246	100.00

TABLE 2.—*Locations Where Incidents Occurred, by Aggregated Employee Job Category in 12 Rural Hospitals in Arizona, 1980 and 1981*

	Job Category						
Location	*Nursing*	*Laboratory*	*Other Technicians/ Therapists*	*House-keeping*	*Physicians*	*Support Staff*	*Total*
Medical/surgical units	83	11	3	24	0	3	124 (50.4%)
Intensive care units	9	1	1	1	0	0	12 (4.9%)
Laboratory	0	20	0	1	0	2	23 (9.3%)
Operating rooms	5	0	6	5	0	0	16 (6.5%)
Emergency rooms	13	3	1	4	1	4	26 (10.6%)
Ob/Gyn units	5	0	0	0	0	0	5 (2.0%)
Radiology	0	0	6	1	0	0	7 (2.9%)
Trash area	0	0	0	10	0	0	10 (4.1%)
Other, or not specified	11	0	6	5	0	1	23 (9.3%)
ALL LOCALES	126 (51.2%)	35 (14.2%)	23 (9.4%)	51 (20.7%)	1 (0.4%)	10 (4.1%)	246 (100.0%)

occurred on the medical or surgical units and 10% in the emergency rooms. For laboratory employees, 31% of incidents took place on the medical or surgical units where technicians perform venipunctures.

Fifteen employees (6.6%) reported more than one exposure incident during the two years. One surgical technician reported three and one laboratory technician reported four. The other 13 employees who reported more than one incident included eight nursing personnel and five housekeepers.

Treatment

Following the reporting of a potential hepatitis B exposure incident, 122 employees (50%) received some type of medical attention. None of the employees was tested for hepatitis B antigen or antibody. In only one incident was the source blood tested for serologic evidence of hepatits B. (Serologic findings were normal.)

Nonspecific treatments given to employees reporting these incidents were first aid (116), eye irrigation (3), antibiotics (2) and sutures (1). One fourth of the treated employees (31) received tetanus toxoid. We could not determine whether the toxoid was given because the incident provided an opportunity for reviewing and updating an employee's immunization status or because the employee was considered at risk of contracting tetanus from the incident.

Seven employees from four different hospitals received immune globulin (IG) following these incidents; one received two doses of IG and the other six received one dose. Three of the twelve hospitals did not stock IG routinely.

None of the employees who reported exposure incidents received hepatitis B immune globulin (HBIG). When requesting information on the availability of HBIG in the hospital, we found that the infection control nurse often was not aware of the product and turned to the hospital pharmacist for information. In some instances the pharmacist also was unfamiliar with HBIG and how it could be obtained. Only one hospital had HBIG available within the facility. Others could order it from a hospital or pharmacy in the nearest city or from the pharmaceutical company representative, but delivery would require one to four days.

Cost

In analyzing the total costs associated with each of these incidents, we included amounts for testing, treatment, work time lost to receive care and charges for the place where care was received. In determining mean costs we considered separately those incidents where some medical care was provided. The results indicate that each incident cost the hospital an average of $32, if all 246 incidents are considered, or $64.50 for the 122 incidents for which some treatment was provided.

Discussion

Incidents that might expose hospital employees to hepatitis B occurred at a rate of 6.3 per 100 employees per year, which is similar to rates reported from urban hospitals and medical centers.[3,4,8,9] In a parallel study in urban facilities in Arizona, we found 7.9 incidents per 100 employees per year. The proportion of incidents in various occupational groups was also similar in urban and rural hospitals, except that reports from housekeepers were more prevalent in the small rural institutions. Housekeepers may be more willing to report accidents in which they are the innocent victims than professional staff who may avoid reporting incidents that could indicate personal carelessness.[9,10]

Reporting may also be influenced by an impression that the risk of contracting hepatitis B is minimal because so few hepatitis patients are admitted to these small hospitals. The fact that two thirds of the hospitals had no known cases of hepatitis B among patients over a two-year period and the absence of any employees with hepatitis B would lend credence to such a perception. The population of rural areas in Arizona does not include many persons in the groups at highest risk of being carriers of hepatitis B antigen—that is, male homosexuals, users of illicit intravenous drugs or persons of Asian extraction.[11] None of the hospitals in our study provided hemodialysis or other specialized services for which hepatitis B is a known problem.

An anecdote that we heard during a visit to one of the sample hospitals provides evidence that opportunities for exposure to hepatitis B patients *do* occur in these facilities. In the one hospital in which there were no reported needle sticks or other incidents, we learned of a potential exposure for which there was no record. The laboratory director recalled that a transient had been admitted through the emergency room with a diagnosis of hepatic shock. Two days later he was discovered to have hepatitis B surface antigen. Upon learning of the laboratory results, the hospital immediately transferred the patient to a large urban medical center and reported the case to the state health department. Our investigation showed that there was no assessment, prophylaxis or follow-up offered to any employees who might have been exposed to the patient while he was in the rural hospital. The hospital stocked no immune globulins and had no written procedures for management of hepatitis B exposures.

In spite of such an occurrence, there was little concern that hepatitis B might be a problem for employees in these rural hospitals. The lack of a written policy for handling needle sticks or other potential exposures to hepatitis B resulted in an absence of medical evaluation or treatment for many employees who reported incidents. Use of immune globulins was infrequent, and HBIG was not readily available in these facilities. Nevertheless, each exposure incident for which treatment was provided cost the hospital an average of $64.50. Use of HBIG would have increased the cost greatly.

These data indicate where cost savings might occur if a hospital were to offer hepatitis B vaccine to employees. Post-exposure efforts to prevent hepatitis B could be decreased if employees were immunized prior to any potential exposure incidents.

The fact that no cases of hepatitis B were reported in the two-year period should not be interpreted to mean that rural hospitals do not have a hepatitis problem. Without conducting a seroprevalence study for hepatitis B markers, we have no information on the possible occurrence of asymptomatic (undetected) or symptomatic (but misdiagnosed or unreported) hepatitis B infections among the employees of these hospitals. Needle sticks and similar accidents occur in significant numbers in all types and sizes of hospitals. The medical staff and administrator of even small institutions should evaluate the potential risk to the hospital's employees and should provide a

written policy for management of such events. The recommendations of the Advisory Committee for Immunization Practices[7,11] should be the basis for the development of such a policy. Although the rate of potential hepatitis B exposure incidents for rural hospitals is similar to that for urban facilities, the absence of a reported, symptomatic case of hepatitis B in a hospital employee included in the survey makes it difficult to recommend indiscriminate preexposure immunization programs for rural hospital employees. Comprehensive and appropriate postexposure prophylaxis for potential hepatitis B exposures is the minimally acceptable standard of care for such events. Preexposure prophylaxis may be justified for subgroups of employees at high risk, but more rigid epidemiologic surveys are needed to define just how valuable and cost efficient such programs would be for very small (fewer than 100-bed) rural hospitals.

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School Screening for Scoliosis

One Experience in California Using Clinical Examination and Moiré Photography

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In 1980 the legislature of the state of California mandated that school screening programs for scoliosis be implemented. This law resulted in variations in methods and efficacy of the programs. One such program using clinical examination and moiré photography was administered to adolescent girls in two secondary schools in Santa Clara County. The findings of 10% of the clinical examinations were ruled to be "positive," 18% on moiré photography alone and 8% on both examinations. The correlation between the two diagnostic procedures was poor (r = .16). Follow-up was done to determine the outcome of the "positive" cases. In all, 25% of the children classified as having scoliosis had no medical follow-up one year from the request by the screening program team. The documented false-positive rate was 15% based on the screening examination. Definitive radiographic evaluation was reported in very few of the positive cases.

Our experience shows the weakness of local programs that have no subject follow-up. It is suggested that public education may be a more effective solution than mass school screening mandates.

(Adler NS, Csongradi J, Bleck EE: School screening for scoliosis—One experience in California using clinical examination and moiré photography. West J Med 1984 Nov; 141:631-633)

Many countries today have school screening programs for spinal deformity. In 1980 California mandated via Assembly Bill 2168 a program of school spinal screening. Implementation and maintenance of the screening was on a local rather than a state level, leading to variation among the programs. We describe our experience with such a program of screening using clinical examination and moiré photography.

In 1973 Minnesota pioneered spinal screening in the United States by implementing a centrally directed, statewide but voluntary program based on clinical examination.[1] Most states now have programs, nine of which are state mandated. Japan is the only nation with a federally mandated screening program, mostly accomplished with surface topography using the moiré technique and low-dose roentgenographic techniques.[2]

Regardless of methods, reports of spinal screening efficacy have largely been encouraging,[3] though some have failed to achieve their goals.[4] Some authors have mentioned that a lack of subject compliance is a complication of mass screening programs.[5,6] This problem is addressed in this report.

Subjects and Methods

In all, 327 girls in grades five through eight of the Santa Clara County Public School System were screened for scoliosis. The screening consisted of a clinical postural examination and moiré photographs.[7] Results were determined to be "negative (normal)," equivocal or "positive (abnormal)" for scoliosis on the postural examination. The moiré photographs were judged by another observer (J.C.) at a later date as positive or negative based on fringe asymmetry.

On the clinical examination standing and bending symmetry was evaluated in the frontal and sagittal planes. A data form was used to record family, personal and medical histories and miscellaneous information in cases ruled positive. Criteria for positive rulings were any two of the following signs: decompensation of head and pelvis, shoulder asym-

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metry, spinous process deviation or a rib hump of at least 0.5 cm. Lesser rib humps and singular postural asymmetries were designated as equivocal signs.

The moiré photography system was a Fujinon FM40 fixed-focus camera mounted on an adjustable tripod. The girls stood in a special purpose positioner that was designed to stabilize standing position by tilting a person 10 degrees anteriorly. The camera was adjusted to the same plane. Positioning was simultaneously monitored by closed-circuit television to ensure correct alignment (Figures 1 and 2). We used 35-mm black and white film to produce prints for future comparison.

Letters were sent to the parents of 70 children in whom clinical examinations showed findings positive for scoliosis, asking that the children have further evaluation for scoliosis by their family physician or an orthopedist. A year later we attempted to determine the outcome of these efforts by sending a questionnaire to those parents.

Results

The incidence of positive and negative findings is summarized in Table 1. Six cases (1.8%) were classified as notable for postural problems other than scoliosis. Four children (1.2%) had pronounced kyphosis and were referred to their physicians. A total of 70 children who had equivocal or "positive" findings on screening for scoliosis or kyphosis were referred to their physicians.

TABLE 1.—*Results of a School Program of Screening for Scoliosis in 327 Adolescent Girls*

	Moiré Photography	
	Positive No. of cases (Percent)*	*Negative† No. of cases (Percent)*
Clinical Examination		
Positive*		
No. of cases (percent)	27 (8.3)	33 (10.1)
Negative†		
No. of cases (percent)	60 (18.3)	186 (56.9)

*"Positive" indicates abnormalities are present that suggest scoliosis.
†"Negative" indicates that results were normal.

The correlation between the screening examination and moiré photography was poor ($r = .16$). This was believed to be because of technical inconsistency in the moiré system, possibly due to moving it between two school sites. Because of this inconsistency, referrals were based on the postural examination only.

Of 70 cases in which referral letters were sent, we received 20 responses to the follow-up letter (28.6%). When known, the physicians who examined the children were contacted for their findings. Of these cases, six were previously classified

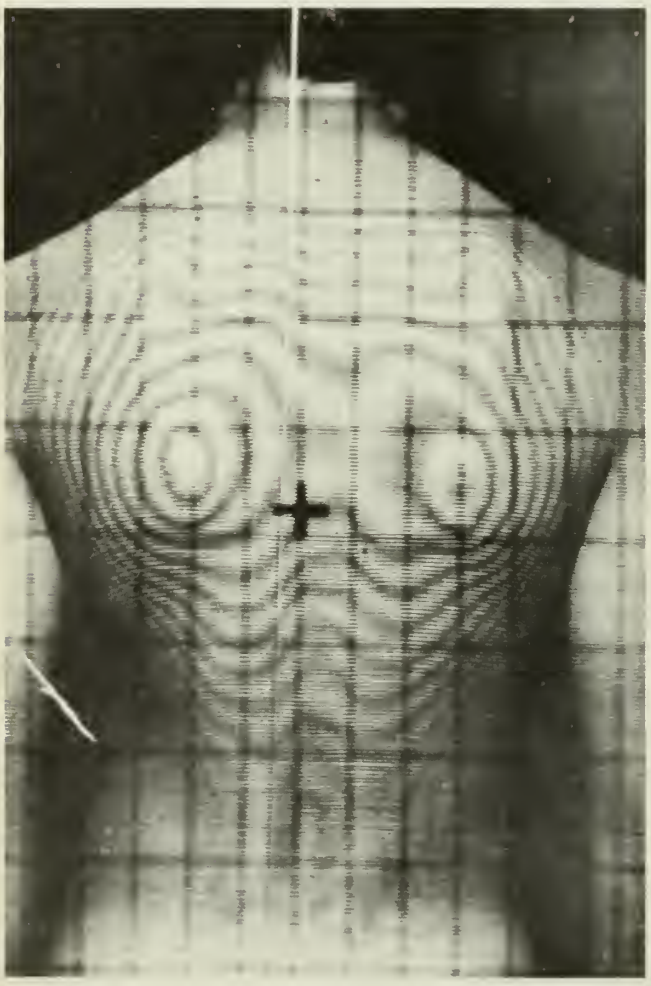

Figure 1.—A moiré photograph showing a normal spine.

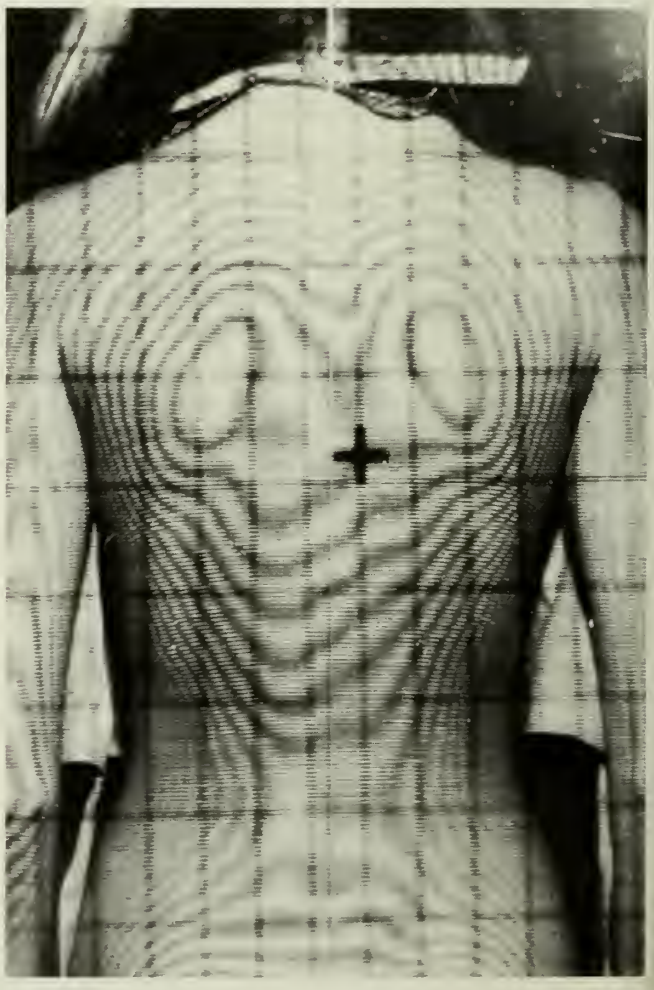

Figure 2.—A moiré photograph of a spine showing abnormal curvature.

as positive on both tests, 11 as positive on screening only and three were equivocal. Five of the responders indicated that a physician had not been consulted. Of the six responses in cases classified as doubly positive (on both clinical examination and moiré photograph), five were diagnosed as scoliosis; one of the patients had not seen a physician. Of the nine cases positive on examination only, two were diagnosed as not having scoliosis and five were diagnosed as having scoliosis; two of the patients had not yet seen a physician. Of the three cases with equivocal responses, two of the patients had not yet consulted a physician; in the other case a diagnosis of scoliosis was made.

Definitive degrees of curvature were reported in only two of the cases, a 31-degree curvature in a girl who had positive moiré and screening examinations and a 20-degree curvature in one with an equivocal examination. Five responses indicated "minor" or "small" curves.

Discussion

Of the 13 children who did have the follow-up examinations as recommended by us one year since the initial screening program, 11 had the diagnosis of scoliosis established; however, the degree of curvature was known in only two patients. The false-positive rate based on the limited responses we received was 15%. Although the correlation between moiré photography and clinical examination was poor, in all cases in which both were positive, scoliosis was confirmed by clinical or radiographic examination.

We could not ascertain the accuracy of scoliosis screening unless complete follow-up data were obtained. In this we were unsuccessful. Only 28.4% of our subject population reported that they had the recommended examination by their physician or available services at the county hospital. Our experience has shown that the mechanics of the screening program are easier to conduct than the most important objective, proper and complete diagnosis and treatment when indicated. Our study indicates inadequate communication between school nurses and parents, and possibly a lack of understanding by parents of the importance of a complete physical examination by a physician to confirm the diagnosis of scoliosis. Perhaps the significance of scoliosis in a growing child was not appreciated by the parents, and insufficient incentive for further follow-up was supplied. Complete follow-up by the school public health staff is compromised by insufficient state funds to back the state mandate. Furthermore, the enforcement of follow-up is ill defined in the law and no provisions for this are established. Should or can we "enforce" follow-up of a non-epidemic, non-life-threatening condition?

In our study we found that the gap between initial screening and follow-up was unacceptable and might have prevented early diagnosis and treatment of children who had a significant degree of scoliosis. Physical examination beyond screening is most important. Even though most cases of scoliosis are idiopathic, it is known that scoliosis can be the presenting sign of a spinal cord tumor and other neurologic and skeletal lesions.

The screening examination is simple and easy to learn. All parents or guardians could do this if they were taught. The promulgation of screening for scoliosis might be better accomplished as a public health measure through the use of spot commercials on television three to four times a year. This type of public health education might relieve the schools of just one additional imposed extracurricular activity and be more cost effective. In the Detroit public school system cost reductions, increased screening accuracy and improved follow-up were reported as a result of thorough parent, child and school staff education.[8] While scoliosis screening programs have been reported as highly successful in smaller, less mobile and more contained populations such as in Montreal,[9] Minnesota[1] and Sweden,[3] in a state as large as California with a highly mobile and varied population, it may not be practical. Finally, in a recent report on school screening,[4] of 31,956 children only 0.3% required treatment. The data of this study did not support the need for a legislated mass screening program based on the criteria of the World Health Organization to use an epidemiologic approach.

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Centruroides exilicauda Envenomation in Arizona

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A retrospective survey of 1,135 telephone calls during 1980 and 1981, reporting scorpion envenomation to the Arizona Poison and Drug Information Center, was reviewed. Of these, 438 calls identified Centruroides exilicauda *as the offending scorpion on the basis of description of the arthropod and consistency of physical findings and clinical course. Envenomation by* C exilicauda *occurred primarily in adults during the summer and early fall months of the year. Although most patients (92%) were treated at home with conservative therapy, 8% of patients either came to or were referred to a medical facility. Children younger than 5 years were frequently brought or were referred to either emergency care or inpatient hospital care. We conclude on the basis of this series that despite the historical reputation of lethality associated with envenomation by* C exilicauda, *most envenomations by this scorpion are relatively minor. The other important observation was that children younger than 5 years appear to be particularly prone to severe toxicity.*

(Likes K, Banner W Jr, Chavez M: *Centruroides exilicauda* envenomation in Arizona. West J Med 1984 Nov; 141:634-637)

Scorpion envenomation is a major reason for telephone calls to the Arizona Poison and Drug Information Center. *Centruroides exilicauda*, the only truly dangerous species of scorpion in Arizona, is distinguished from other genera by its slender body (Figure 1) and a small tubercle at the base of the stinger.[1] Patients envenomated by this scorpion have a distinct and typical clinical course including local pain, numbness or hypoesthesia, increased salivation, agitation, wheezing, tachycardia, hypertension and muscle spasm. Previous reports of cases have been based on physician contacts, clinical experiences and hospital populations.[2-4] A retrospective review of two years of telephone calls from patients envenomated by this scorpion was undertaken to evaluate the clinical course of these patients and to establish a basis for improved management.

Methods

A total of 1,135 cases of scorpion envenomation reported during the years 1980 and 1981 to the Arizona Poison and Drug Information Center in Tucson were reviewed. The following information was extracted from the poison control form: age, sex, preexisting medical conditions, current medications, time of exposure, description of scorpion, home management (analgesics, cold pack, antihistamine), description and duration of pain and emergency room or physician treatment. Patients were called at 1, 5 to 8, and 24 hours, with additional calls at 24-hour intervals if symptoms persisted. Those patients with signs of local ecchymosis, erythema and swelling were eliminated from the series as not having symptoms consistent with a diagnosis of *C exilicauda* envenomation. Envenomated patients with the typical syndrome of *C exilicauda* sting were included even if a detailed description of the scorpion was not available.

Figure 1.—*Centruroides exilicauda* showing the typical slender pincers and tail segments. (Photograph courtesy of Findlay Russell, MD, PhD.)

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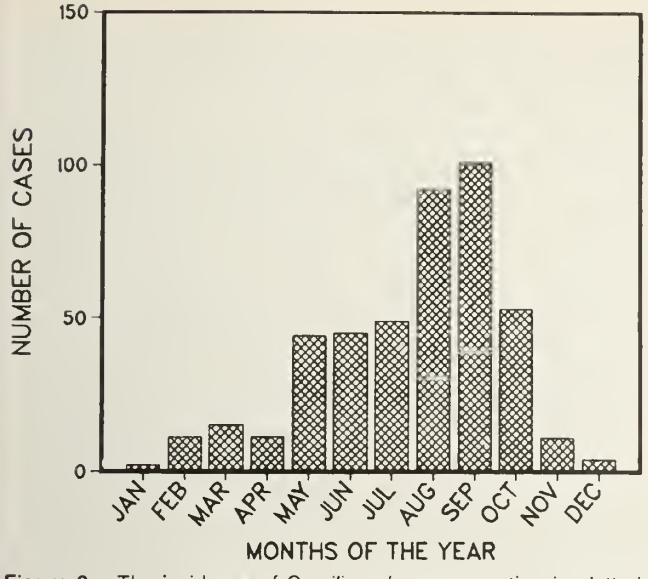

Figure 2.—The incidence of *C exilicauda* envenomation is plotted as a function of reporting month from a series of 438 cases reported to the Arizona Poison and Drug Information Center.

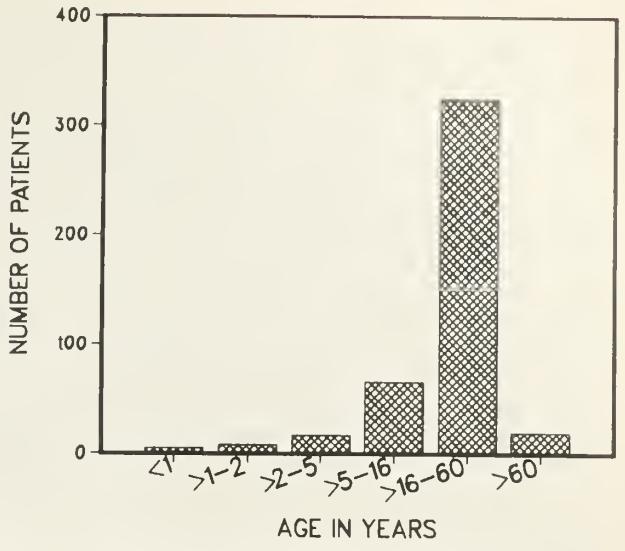

Figure 3.—The age distribution of patient contacts is shown for envenomation by *C exilicauda* in Arizona.

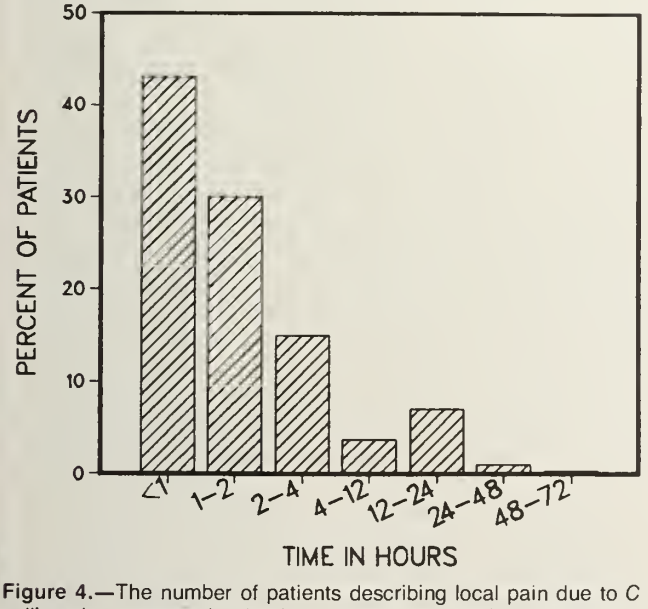

Figure 4.—The number of patients describing local pain due to *C exilicauda* envenomation is shown versus the maximal duration of this symptom in hours.

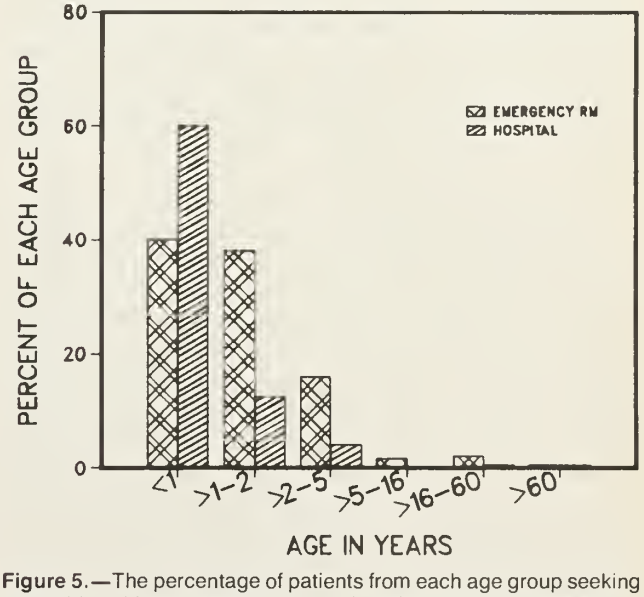

Figure 5.—The percentage of patients from each age group seeking or requiring either emergency room or inpatient hospital care is shown as a distribution of age in years.

Results

The 1,135 calls reviewed were widely distributed throughout the state. Of these, 438 were identified as being caused by *C exilicauda* envenomation. Monthly distribution of stings showed a high prevalence in the summer and early fall months (Figure 2). The age range of patients was from 6 months to 81 years with a distribution favoring the adult age group from 16 to 60 years (Figure 3). There was a slight predominance of male patients, 245 compared to 193 females.

The most common symptom was local pain (70%) with sensory abnormalities in the extremities reported in 234 patients. The majority of patients had a relatively short duration of pain (less than 4 hours) (see Figure 4). In a subjective description one patient described the pain as severe, seven patients described it as moderate and the remaining 300 patients as mild.

Agitation or hyperexcitability was described for 5% of the patients. The group younger than 2 years, however, had an 80% incidence of hyperexcitability. The finding of hyperexcitability was described in all children younger than 1 year. The envenomation was located on the foot in 52% of cases and on the hand in 40%. The remaining 8% had various contact points. Eight of the 438 patients had been stung more than one time.

In all, 92% of the patients were treated conservatively in the home. The remaining 8% either were referred for medical care or came themselves to a medical facility. As can be seen in Figure 5, there was an age-related variability in the number of patients receiving medical care. All patients younger than 1

year were either admitted to hospital or seen in an emergency facility. In the 1- to 2-year and the 2- to 5-year age groups a similarly high rate of either emergency room or inpatient hospital care was evident.

Those patients who stayed at home used mild analgesics and local cold compresses for discomfort. Among the group seen either by private physicians, at emergency facilities or in a hospital, various regimens were prescribed. In patients admitted to hospital, phenobarbital was given for agitation or hyperactivity, and one patient, 2 and a half years of age, also received calcium gluconate, which was reportedly effective in relieving muscle spasms. One man admitted to hospital (age 39 years) was given scorpion antivenin prepared from goats for bradycardia, hypertension and laryngeal spasm. In this single case the symptoms reportedly abated within one hour. Emergency room treatment included observation, cold compresses and nonnarcotic analgesics; however, one patient was given phenobarbital and two patients received diphenhydramine.

Discussion

There are 650 known living representatives of scorpions, divided into six families. In North America all of the dangerous species are in the family Buthidae. *C exilicauda* is one of the neurotoxic species of this family and inhabits Arizona, western New Mexico, California, parts of Texas and northern Mexico.[5] *C exilicauda* shows much interpopulation variability and is now believed to be synonymous with *C sculpturatus*.[6]

The original description of *C sculpturatus* by Ewing was based on two adults and two immature specimens collected in 1927 at Tempe, Arizona.[7] Ewing described the general color of this species as yellowish brown with no dorsal stripes, spots or other markings. Stahnke[8] described a new species with two dark dorsal stripes, which was found in the same general areas as *C sculpturatus* and was named *C gertschi*. Laboratory studies soon showed, however, that venom of this species was almost identical, both from a biochemical viewpoint and in toxicity, with that of *C sculpturatus*. The name *C gertschi* was abandoned. Later, Stahnke found that litters produced by patternless scorpions also contained striped individuals. Further study revealed that *C sculpturatus* was actually represented by four color phases ranging from the characteristic unpatterned straw color to striped specimens.[7]

Williams[6] compared *C exilicauda* from Baja California with *C sculpturatus* from Tempe, Arizona, and found only insignificant differences in morphology, reflecting only local racial adaptations. Upon evaluating the taxonomic characteristics of *C exilicauda*, Williams observed that species are generally darker when taken from habitats with dark substrate and lighter when taken from habitats with light substrate.[6] Also, a difference in body size was noted in *C exilicauda* from different regions.[6]

Scorpions are arthropods that have a hard exoskeleton. The cephalothorax is covered dorsally by a shield called the carapace and has a powerful pair of pincers anteriorly. The preabdomen consists of seven segments and the postabdomen, or tail, consists of six segments.

The sixth segment of the tail is a bulbous enlargement called the telson, and tapers to a stinger. Within the telson are two venom glands with independent ducts leading to an opening near the stinger,[9] and secretion of the venom is of apocrine type. *C exilicauda* can be differentiated from other species by the presence of a small subaculear tooth (tubercle or hair) at the base of the stinger.[3]

The size of *C exilicauda* ranges from about 1.3 cm when the young leave the mother's back to about 7.6 cm when they are fully grown. *C exilicauda* are sometimes called "bark" scorpions because of their favored habitat under the loose bark of trees and in crevices of dead trees and logs. The bark scorpions characteristically rest their tails on the substrate while ground scorpions arch the tail over their back. *C exilicauda* have a negative geotaxis which enables them to cling to ceilings and the underside of objects.[10] Therefore, many people are stung as they pick up objects they have failed to look under, or when they attempt to pick scorpions off of walls and ceilings. The species is nocturnal and the greatest activity is at night. During the day they seek out moist, cool microhabitats under lumber piles, bricks, stones and debris. They may crawl into houses and hide under clothing, in shoes or in other objects.

Scorpions are predacious, feeding for the most part on insects and other arthropods; prey is usually grasped with the pincers and stung by means of the scorpion arching its postabdomen over its own head. The prey is then torn and crushed with the mouth parts; only the liquified tissue is ingested. Solid material is ejected as small pellets.

Scorpion envenomation from *C exilicauda* is a very common occurrence in the southwestern United States from April to November. Although there are more than 20 species of scorpions recorded in Arizona, *C exilicauda* is quite distinguishable from the nonlethal species. The base color of the body is pale to golden yellow (straw colored). The entire body (especially the joints of the legs, pincers and tail) is long and slender. This is in contrast to the stubby or chunky appearance and darker color of many other species.

C exilicauda venom contains vertebrate neurotoxic proteins.[11-13] The venom is thermostable and the composition varies with the season, age and nutritional state of the scorpion.[14]

The minimum lethal dose of *C exilicauda* venom in mice is 1.12 mg per kg of body weight,[15] placing this venom among the most potent animal venoms.[16] Following envenomation, phenomena generally appear in order: immediate local pain, hyperexcitability, increased salivation, increased respiration, muscle twitching and contractions leading to convulsions, spastic paralysis and respiratory failure, which may occur from a few minutes to several hours after the sting.[17]

General neurotoxicity is of an excitatory nature, including the autonomic (parasympathetic and sympathetic) as well as the skeletal neuromuscular systems as observed from human and animal envenomation.[17] The most common parasympathetic symptoms include salivation, lacrimation, sphincter relaxation, gastric hyperdistension, bradycardia and hypotension. The typical sympathetic symptoms include mydriasis, piloerection, perspiration, hyperglycemia, tachycardia and hypertension. The effects on the skeletal muscle are indicated by twitching, spasms and muscle contractions.[17]

Cardiovascular effects include an initial increase in cardiac output, tachycardia and hypertension followed by arrhythmias, bradycardia and hypotension.[18,19] Hypertension is a very characteristic effect of all buthid venoms and has been

observed in humans and a wide variety of laboratory animals.[17] Tachycardia is caused by the release of catecholamines from sympathetic nerve terminals, which is a result of preganglionic, ganglionic or postganglionic stimulation or of sympathetic stimulation of the adrenal gland. Bradycardia has been reported to be due to the release of acetylcholine by action on vagal ganglia and postganglionic nerve endings in the heart.[20]

Laboratory animals injected with *Centruroides* venom demonstrated respiratory irregularities expressed by the intermingled irregularities in rate, with periods of apnea and an increase in depth.[21] Higher doses resulted in respiratory paralysis in the expiratory position. Bronchiolar obstructions caused by secretions and laryngeal and bronchiolar muscle contraction are common manifestations of scorpion envenomation that contribute to respiratory distress.

Epidemiologic studies involving venomous animals are often hampered by an inability to obtain the specific animal for identification. In the case of the scorpion, *C exilicauda,* this problem is lessened by the relatively specific symptoms produced by the species. By not including patients with local swelling, erythema or ecchymoses typical of other local scorpions, a group of patients can be identified for study.

The present series represents a large sampling of patients in and out of hospital. One unexpected finding in this study was the large number of scorpion contacts in this state. In a previous publication on *C exilicauda,*[3] this arthropod was reported as the most lethal venomous animal in Arizona. Since 1960 the incidence of death following scorpion envenomation has steadily declined, despite an increase in the population of the state, leading one author to suggest that the decrease may be related to less reliance on drugs such as meperidine chloride and amobarbital.[3] The last verified death from a scorpion sting in Arizona was in 1968, in a 5-month-old infant (F. E. Russell, MD, PhD, oral communication, January 1983). The present study indicates that the vast majority of scorpion contacts is not serious. Indeed, no lethal cases were reported. The majority of scorpion envenomations occurred in adults, and reactions were minor.

This study clearly identifies the group of those under 2 years of age as being at high risk for requiring hospital admission. These data may be biased by a failure to recognize milder envenomations in this age group unless the scorpion is observed. The report of Rimsza and associates[2] of a series of patients admitted to four hospitals in the Phoenix area over an eight-year period is consistent with the present findings. In their series of 24 patients, 80% were younger than 10 years and 85% had symptoms of severe agitation.

Since one of the purposes of this study was to develop management protocols for telephone contacts involving scorpions, we conclude the following:

- The majority of *C exilicauda* envenomations occur in adults. The symptoms are pain, hypoesthesia or paresthesia of less than four hours' duration. These patients can be safely managed in the home with simple symptomatic measures.
- Children younger than 2 years suffering from a sting by this scorpion are often agitated or hyperexcitable and frequently require admission to hospital.
- Despite the historical suggestion of high lethality associated with Arizona scorpions, no deaths occurred in this series.

It is clear that further study on the management of scorpion envenomation is indicated. There is no consensus on the medical treatment of these envenomations. Controversial questions such as the use of antivenin, phenobarbital and calcium gluconate for scorpion envenomation remain unresolved, and further studies should stress documentation of both the safety and efficacy of these therapeutic approaches.

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Medical Progress

Magnetic Resonance Imaging Part II—Clinical Applications

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Magnetic resonance (MR) imaging is the most promising new technology to appear in the clinical imaging arena since the advent of x-ray transmission computed tomography in the early 1970s. Five independent tissue characteristics (spin density, spin-lattice and spin-spin relaxation times, flow and spectral shift information) are accessible to MR imaging, and their relative influence in the magnetic resonance image can be varied by appropriate selection of pulse sequences and pulse times. All major organ systems appear to be amenable to MR imaging, and some are revealed with superior definition compared with their appearance in images obtained by alternate imaging technologies. Of particular interest is the superior contrast resolution in MR images of the brain and spinal cord, and the absence of bone- and motion-induced artifacts in images of the abdomen and pelvis. Applications of MR imaging to the heart and great vessels are just developing, as are new types of contrast agents for use in MR imaging. In vivo chemical spectroscopic measurements by magnetic resonance are heralded by some investigators as the most significant contribution that magnetic resonance will make ultimately to clinical diagnosis.

At present, the number of MR imaging units is extremely low, and clinical studies are proceeding at a slow rate. Nevertheless, it is possible to provide a preliminary evaluation of the usefulness of MR imaging in a variety of clinical applications. This article is such an evaluation, tempered by the acknowledgement that much additional work remains to be done.

(Hendee WR, Morgan CJ: Magnetic resonance imaging. Part II—Clinical applications [Medical Progress]. West J Med 1984 Nov; 141:638-648)

To date, a few thousand patients have been examined with magnetic resonance (MR) imaging and major diseases in almost all organ systems have been demonstrated. Based on this work, it is possible to speculate, within limits, on what MR imaging does better than, as well as and not as well as x-ray transmission computed tomography (CT) does, especially for neurological disease. Computed tomography provides excellent visualization of tumors, abscesses, hemorrhage and hydrocephalus; MR imaging does a comparable job with these conditions, sometimes yielding more information and sometimes less.

The ability to make axial, coronal and sagittal sections with MR imaging facilitates the visualization of the full extent of disease without having to infer it from images made in a single orientation. The detail in nonaxial MR imaging sections is much better than that in reformatted CT images (Figure 1). These sections should be particularly helpful in planning biopsies and in radiation therapy. One of the limitations of CT work is the loss of information in coronal sections because of dental artifacts and patient motion; these should be less troublesome with MR imaging.

Compared with x-ray attenuation, variations in proton density, spin-lattice relaxation time (T_1) and spin-spin relaxation time (T_2) provide improved soft tissue contrast aided frequently by blood flow. This advantage often more than compensates for the slightly reduced spatial resolution of MR imaging compared to CT. MR imaging shows muscle, fat and blood vessels as very different soft tissues (Figure 2), and images of the brain can be resolved into gray and white matter with unique clarity, particularly in T_1-weighted images (Figure 3). MR imaging is as accurate as CT in demonstrating space-occupying lesions and probably surpasses it in re-

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
CT = computed tomography
MR = magnetic resonance
MS = multiple sclerosis
T_1 = spin-lattice relaxation time
T_2 = spin-spin relaxation time
TMR = topical magnetic resonance

vealing small lesions, infiltrating tumors and early changes of inflammation.

Clinical Applications

The superiority of MR imaging in detecting small, focal lesions is best demonstrated in multiple sclerosis (MS) (Figure 3). With MR imaging it may be easier to diagnose MS earlier and with greater certainty.[1] One problem with MS is that lesions may be present without clinical manifestation until a substantial portion of white matter is involved. Detection of these lesions may permit treatment before the disease has progressed very far and may also provide a better way of assessing the effectiveness of treatment. At this time, the clinical impact of MR imaging on MS has yet to be determined.

Brain-stem infarction is often difficult to see with CT unless the whole vertebrobasilar circulation is impaired and the entire pons is swollen, usually preterminal events. A brain-stem stroke of lesser magnitude can present significant clinical signs and yet not be visible with CT. Approximately 80% of brain-stem infarctions (Figure 4) are visible with MR imaging because of its better contrast and the lack of the artifacts from bone around the posterior fossa present with CT.[3] Flowing blood in the venous sinuses is signal free; this blood helps to outline the posterior fossa and to show cerebellar lesions and atrophy.

The edema of an early infarction appears black on an inversion recovery scan and white on a spin-echo scan, and is more visible with MR imaging than with CT. Although the evidence is incomplete, the increased soft tissue contrast of MR imaging and its ability to show subtle structural changes may permit earlier detection of infarction with MR imaging. Infarctions have been visualized within six hours of production, and they possibly could have been detected earlier.[4] Generally, the edema seen in hemispheric infarction is more extensive in MR images than in CT scans. The same conclusion appears to be valid for systemic lupus erythematosus and herpes encephalitis[5] (Figure 5) and earlier detection of these conditions may be possible with MR imaging.

Although CT demonstrates acute hemorrhage much more readily than MR does, demonstration of chronic subdural hematomas and intracerebral hemorrhage is superior with magnetic resonance. Chronic blood collections are visible as white areas in both inversion recovery and spin-echo images. The central liquefaction of an aging cerebral clot, sometimes noted at autopsy but invisible on CT scans, has been seen on

Figure 1.—Sagittal and coronal sections of the brain. These views show a variety of structures clearly. The cerebellum, entire brain stem, third and fourth ventricles and cisterns are particularly clear. Note the fifth cranial nerve in the coronal section **(arrow)** (reproduced with permission from General Electric Co, copyright, 1983).

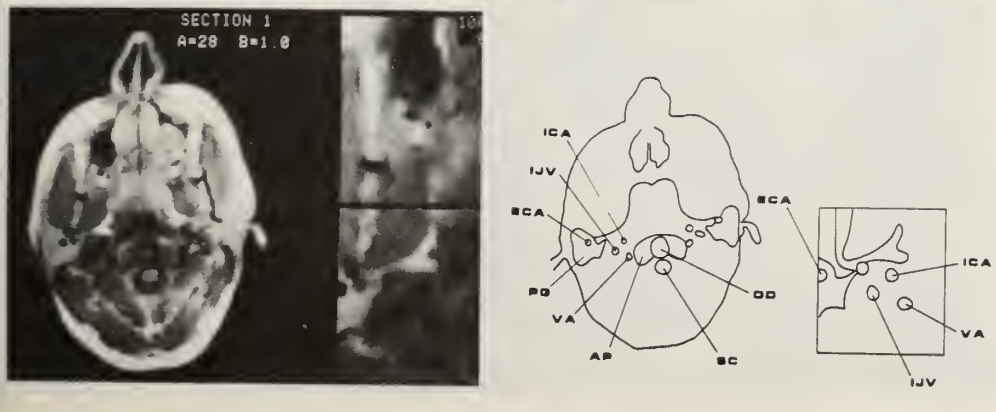


Figure 2.—Upper neck: spin-echo scans. The internal carotid artery **(ICA)**, internal jugular vein **(IJV)**, external carotid artery **(ECA)**, vertebral artery **(VA)**, articulating process of C_1 **(AP)**, spinal cord **(SC)** and odontoid process **(OD)** are all clearly shown. Also shown is inflammatory disease of the maxillary sinus (not labeled) (from Crooks et al[2]).

some inversion recovery scans, a further demonstration of the superior soft tissue contrast of these images. A chronic subdural hematoma that is isodense on CT examination is much less likely to be missed with MR imaging. Not only does it appear whiter than adjacent brain parenchyma on both inversion recovery and spin-echo scans, but also displacement of the cortex away from the inner table is easier to appreciate with MR imaging because of the contrast between subdural and cortical gray matter.[2]

Primary and metastatic brain tumors and the edema around them tend to have long T_1 and T_2 values; these lesions usually appear dark on inversion recovery scans and light on spin-echo scans, as explained earlier in the discussion of scanning methods.[6] Tumors appear in greater contrast to normal parenchyma with MR imaging, compared with CT. Patients with low grade astrocytomas may have a normal CT; however, these patients will almost always have abnormal MR images. One problem created by the sensitivity of MR imaging to edema is that the boundary between a tumor, metastasis or abscess and the surrounding edema is not shown as clearly with MR imaging as with contrast-enhanced CT (Figure 6). The development of contrast agents suitable for MR imaging may help resolve this problem.

Figure 7 demonstrates dark areas within the brain stem in an inversion recovery image. These areas are thought to represent changes associated with Parkinson's disease; it has not been possible to see such changes with CT. The significance of this finding is not clear, but the ability of MR imaging to reveal brain-stem structures not visible before may produce unexpected information about a variety of diseases. MR imaging permits direct imaging of brain myelinization in neonates and infants for the first time (Figure 8). This finding may have impact upon study of the effects of malnutrition, hypothyroidism and phenylketonuria on myelinization.[8]

In MR imaging studies of gray matter disease, the relatively long T_1 of gray matter must be considered together with

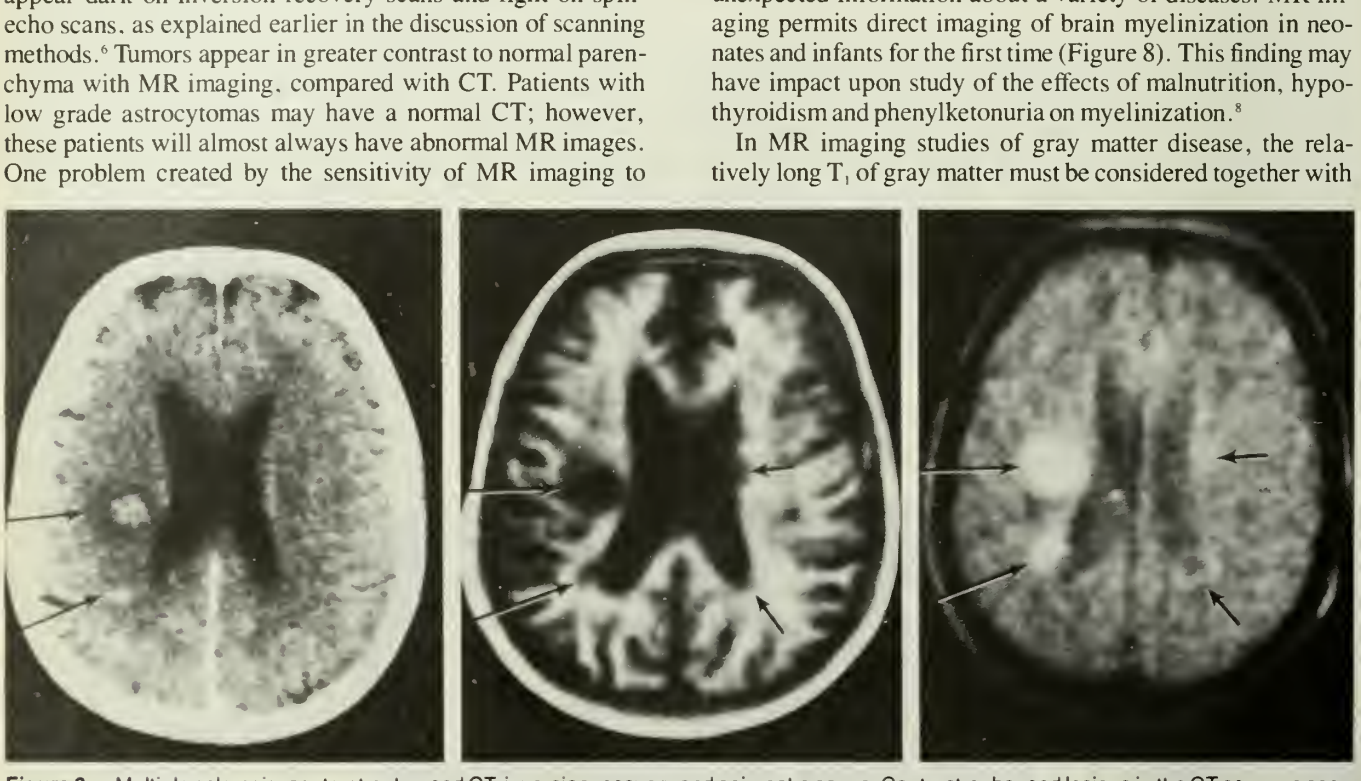


Figure 3.—Multiple sclerosis: contrast-enhanced CT, inversion recovery and spin-echo scans. Contrast-enhanced lesions in the CT scan are seen in both MR images **(long arrows)**. Two other lesions were demonstrated only with MR imaging **(short arrows)** (from Bydder et al[3]).

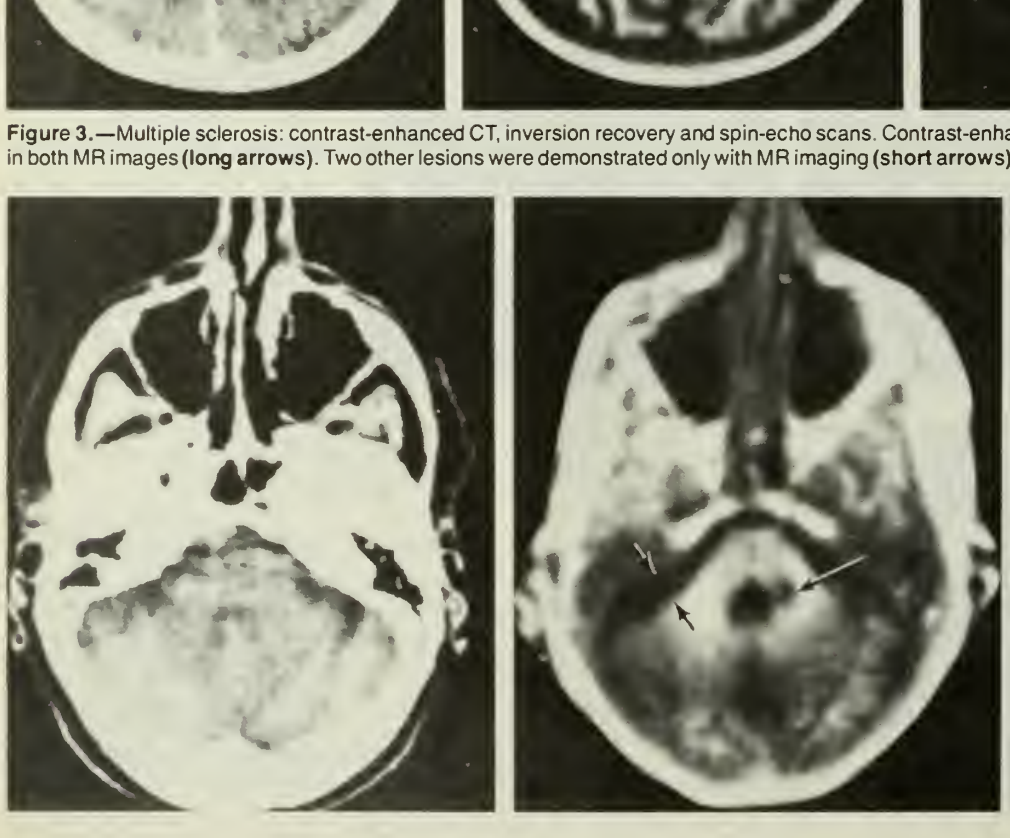


Figure 4.—Brain-stem infarction and cerebellar atrophy: CT and inversion recovery scans. The area of infarction appears dark **(long arrow)** and there is probable cerebellar atrophy **(short arrows)** (from Bydder el al[3]).

the perturbing influence of partial volume effects. In inversion recovery scans, the gray regions around the sulci represent an averaging of superficial white matter, gray matter and adjacent cerebrospinal fluid. Partial volume effects can produce apparent lesions in the normal white matter of the hemisphere or brain stem because of the cerebrospinal fluid surrounding these areas. Most lesions have a prolonged T_1 and are dark in T_1-weighted images; hence, tumors or infarctions on the periphery of the brain stem could be missed because they do not contrast with cerebrospinal fluid in the subarachnoid space. Such lesions are more visible in spin-echo images because their prolonged T_2 makes them appear white.[9]

The extent of head and neck tumors may be more apparent in MR images than in CT images. It is hoped that MR imaging will be more sensitive in detecting tumors that are infiltrative but that do not displace normal structures. Displacement of major vessels by the tumor is easier to see with MR imaging than with CT, and the sensitivity of MR imaging to changes in blood flow can occasionally add information about the involvement of major vessels (Figure 9). Although this modality may be useful in staging head and neck tumors[11], its real value is still unknown.

Images of thoracic structures suggest that hilar masses such as primary lung cancer can be distinguished from the vascular structures of the hilum because the natural contrast of blood flow makes the vessels dark (Figure 10) and MR evaluation of the hilum is promising. However, small peripheral metastatic nodules may not be as visible with MR imaging as with CT. Cardiac motion causes some loss of spatial resolution in MR imaging and may introduce minor motion artifacts. Because of the blurring effect of motion, the signal obtained during active contraction of the myocardium contributes relatively little to the final image. Hence, magnetic resonance images reveal the heart in diastole with some loss of resolution. Further detail can be obtained with gated cardiac MR imaging studies in which data are accumulated during 50-millisecond portions of the cardiac cycle. This technique yields images with excellent resolution and includes the valves and papillary muscles (Figure 11). Gated coronal sections may demonstrate cardiac anatomy well enough to diagnose congenital heart disease. Septal defects, single ventricles, outflow obstructions, anomalies of the great vessels and irregularities of blood flow may one day all be able to be diagnosed by MR imaging.[13]

Atherosclerotic plaques in excised vessels can be visualized by MR imaging (Figure 12). If this capability can be developed in vivo, MR imaging could be used to evaluate atherosclerotic lesions, to assess the effectiveness of experimental treatments and to identify patients who need angiography by revealing asymmetry of blood flow between the left and right carotids.[10] According to recent reports, MR imaging also promises to yield superior visualization of myocardial infarction.[14] At present, the coronary arteries are not easily visualized in vivo by MR imaging, and it is too early to predict if this will ever be possible.

Early CT images of the abdomen were severely degraded by respiratory motion, and it was not until scan times were reduced to a few seconds that abdominal CT images became acceptable. Even though MR image scan times are long, motion does not present as much of a problem because the images primarily represent the abdomen at rest between inspiration and expiration (Figure 13). Compared with CT, MR imaging presents a greater number of vascular structures to provide more anatomic markers. The ability to reveal blood vessels and to provide images in nonaxial planes should increase the contribution of MR imaging to the diagnosis of conditions as

Figure 5.—Herpes encephalitis: CT, inversion recovery and spin-echo scans. Although all images show edema of the medial temporal lobes, it is easier to see with MR imaging. The spin-echo image **(right)** best shows the extent of disease (from Bydder[7]).

Figure 6.—Metastatic carcinoma of the cervix: CT, inversion recovery and spin-echo scans. All three images show an abnormality, but only the contrast-enhanced CT **(left)** shows the metastasis separate from the surrounding edema (from Bailes et al[5]).

diverse as aortic aneurysms, portal hypertension and invasion of the vena cava by hypernephroma. In particular, the role of MR imaging in detecting aortic aneurysms is very encouraging.[15]

Some tumors visible with CT cannot be seen with MR imaging and vice versa (Figure 14). This finding suggests a complementary role for CT and MR imaging in the abdomen. Small metastatic foci (Figure 15) and large tumors (Figure 16) can be seen with both MR imaging and CT. MR imaging is at least as accurate as ultrasound or a radionuclide liver scan in detecting metastases, and may be superior in evaluating cystic masses because it can better differentiate benign cysts from tumors with a necrotic center.[17] Gallstones are not routinely visible with MR imaging, but its ability to demonstrate edema in and around the wall of the gallbladder may aid in the diagnosis of cholecystitis.[17] Diffuse liver diseases without focal structural change (for example, fatty infiltration and some cases of cirrhosis) may be more visible with MR imaging than with CT (Figure 17). Obstructed bile ducts can be differentiated from portal and hepatic veins because of blood flow in the veins.

Although the normal pancreas can be difficult to visualize with MR imaging because of its isointensity with surrounding structures, recent studies suggest that it can be revealed by careful selection of the imaging techniques.[18] Diseased pancreas more frequently is visible (Figure 18). Carcinoma can usually be distinguished from pancreatitis by a prolonged and nonuniform T_1 and irregular shape.[20] Pancreatic carcinoma that is not associated with obstructed bile ducts can be hard to differentiate from enlarged mesenteric nodes.[20] Overall, MR imaging may be more accurate than ultrasound in diagnosing pancreatic disease, and neither an overlay of bowel gas nor variations in technical expertise affect the adequacy of the examination.[20]

The renal cortex, medulla and collecting systems can be seen as separate structures in MR imaging (Figure 19). MR imaging can distinguish between pelvicalicectasis due to obstruction and that due to reflux; in reflux, the cortex and medulla are still visible as separate structures, while in obstruction, they cannot be distinguished.[21] MR imaging appears to be equivalent to contrast-enhanced CT in evaluating the level of ureteral obstruction. MR imaging is equivalent to

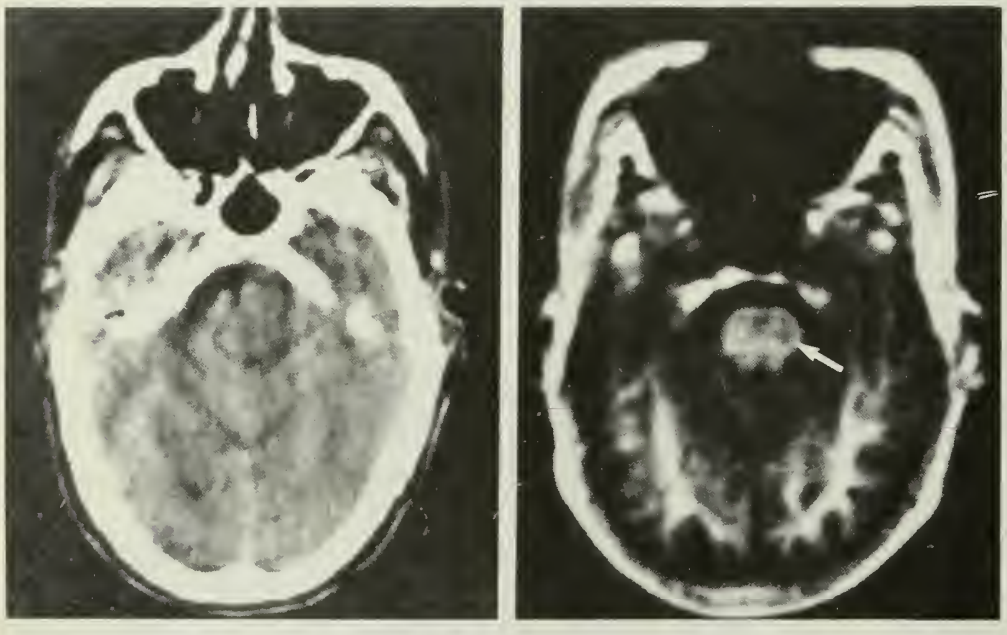


Figure 7.—Parkinson's disease: CT and inversion recovery scans. This disease is characterized by irregular dark areas **(arrow)** within the substantia nigra of the midbrain on the inversion recovery scan **(right).** The CT scan does not reveal these areas (from Bydder et al[3]).

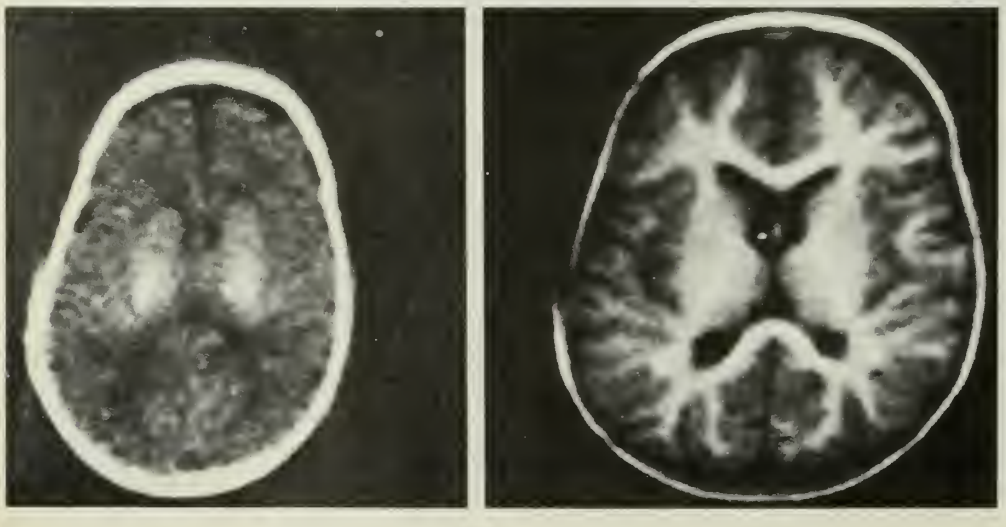


Figure 8.—Normal myelinization: inversion recovery scan. Myelinization has occurred only deep in the brain, in the region of the posterior limb of the internal capsule, in a month-old infant **(left).** More extensive myelinization is present in a year-old infant **(right)** (from Bydder[7]).

ultrasound in detecting and identifying cysts and may be somewhat better than ultrasound in certain cases of polycystic disease because it can more readily distinguish hemorrhagic and infected cysts.[21] MR imaging is equivalent to CT in differentiating solid from cystic masses and may be superior to CT in differentiating certain cysts from renal pelvic lipomatosis.[21]

Nonproton MR Imaging and Spectroscopy

Elements other than hydrogen exhibit nuclear magnetic resonance if they have an unpaired proton, an unpaired neutron or both. Many elements have at least one isotope that fulfills these criteria. To be useful for magnetic resonance, however, the isotope must yield a detectable signal. For any particular material, the signal strength depends upon the signal magnitude from the isotope of interest and the concentration of the isotope in the material. With the exclusion of hydrogen, phosphorus 31, carbon 13, sodium 23 and fluorine 19 are the most promising isotopes for MR imaging analysis. In biological materials, all yield a signal which is 1/5,000 or less intense than that from hydrogen, in part because these isotopes are present at much lower concentrations in tissues and in part because they yield a weaker signal than hydrogen. In general, these isotopes require magnetic fields of 1.5 T and above to yield signals strong enough to be extracted from noise. At a given field strength, the resonance frequencies of these isotopes are lower than that for hydrogen. Because of the poor signal-to-noise ratio, images of these isotopes that have been obtained to date have unacceptably poor resolution. Many investigators feel that images of elements other than hydrogen will never be clinically useful and that magnetic resonance analysis of these elements will be confined to spectroscopic measurements rather than imaging studies.

Biochemical analysis has been the most important work conducted to date with elements other than hydrogen. This application relies on the phenomenon of "chemical shift," caused by the slight influence of electrons on the magnetic field intensity experienced by the sample. The perturbing effect of the electrons depends on the specific chemical bonds in which the isotope of interest is involved. Slight changes in resonance frequency caused by chemical shifts are very small and detectable only in very strong and pure magnetic fields. Chemical magnetic resonance work requires a magnetic field homogeneity much better than that required for proton imaging. At present, these technical problems are overcome best

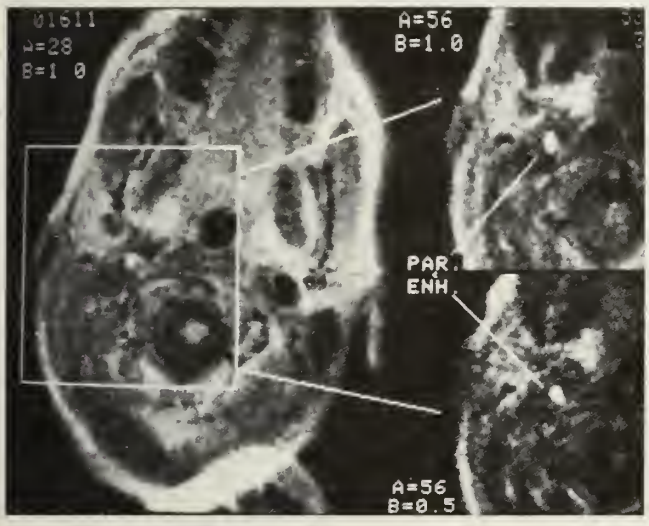


Figure 9.—Partial obstruction of jugular flow by neck tumor. The tumor is not present in this section, but its effects on blood flow highlight the internal jugular vein on the affected side. These three spin-echo images differ from each other only in the interpulse delay time. The increased enhancement in the right-hand images **(PAR ENH)** indicates that flow is impaired but not fully obstructed (from Kaufman et al[10]; by permission of the American Heart Association, Inc).

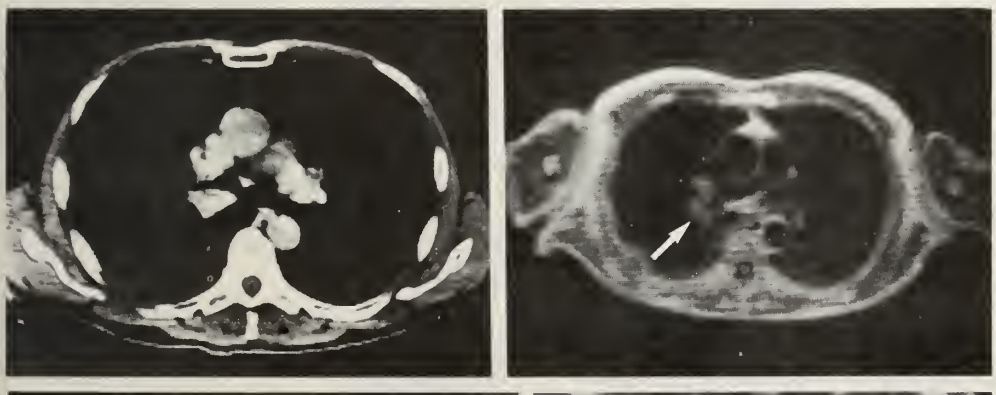


Figure 10.—Bronchiogenic carcinoma: CT and nuclear magnetic resonance scans. In the nuclear magnetic resonance image, blood flow in the great vessels makes them appear dark and the tumor mass **(arrow)** is more visible. The CT scan **(left)** yields confusing soft tissue densities (from Alfidi et al[12]).

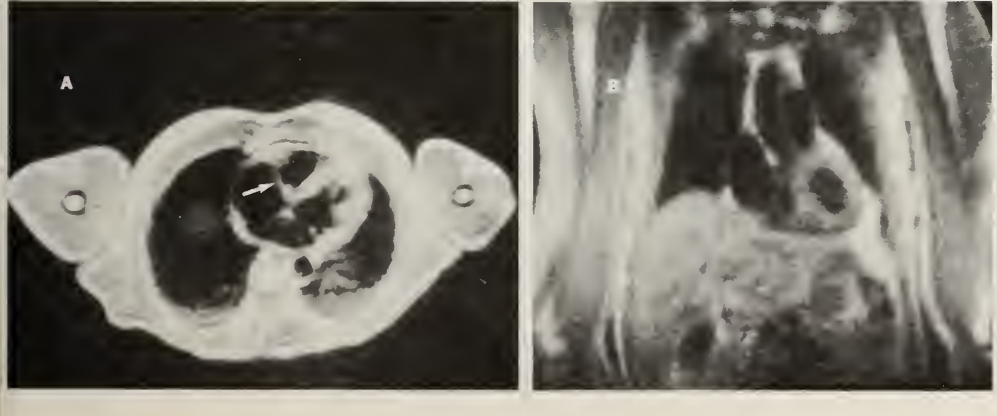
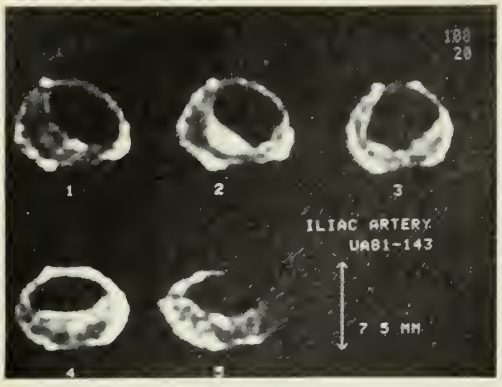


Figure 11.—Axial **(A)** and coronal **(B)** sections of the normal heart: Gated MR during systole. The axial section shows the tricuspid valve **(arrow)** and white areas in the left ventricle that represent papillary muscles. The coronal section provides a unique perspective of cardiac anatomy (reproduced with permission from Technicare Corp).



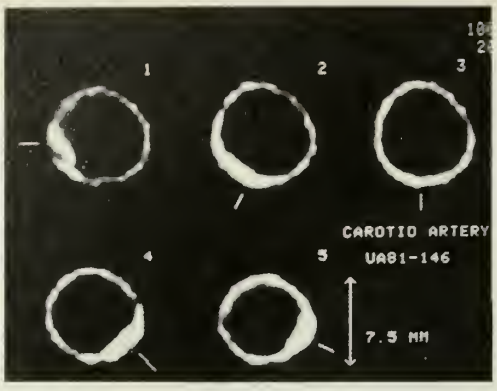


Figure 12.—Atherosclerotic plaques: Images of contiguous sections of excised arteries. In the iliac lesion, two separate components are visible. Dense connective tissue appears dark (sections **1, 4, 5**) and surrounds a lipid portion which appears white (sections **2, 3**). The mixture of connective tissue and lipid portions signifies advanced disease. The carotid lesions contain a more homogeneous blend of lipid and connective tissue (from Kaufman et al[10]; by permission of the American Heart Association, Inc).

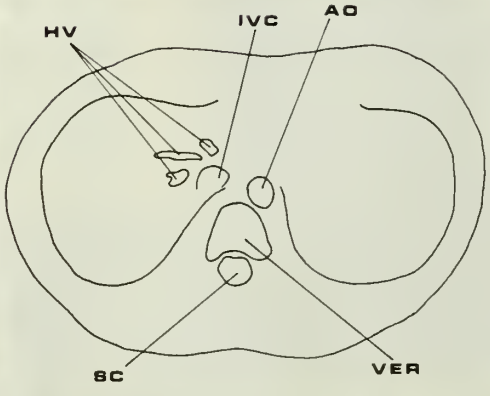
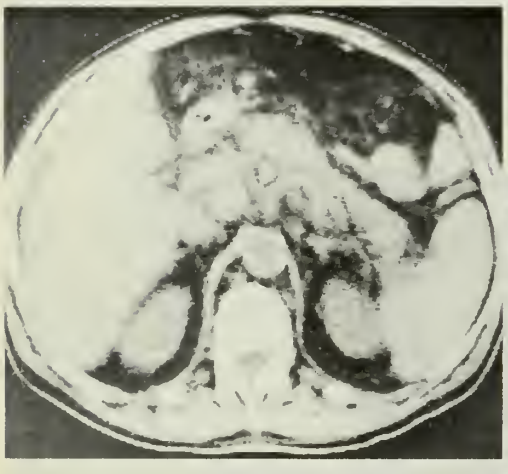


Figure 13.—Normal upper abdomen at the level of the diaphragm. MR images contain no motion-induced streak artifacts. Here, the soft tissue detail is good, despite respiratory motion. The hepatic veins **(HV)** radiate towards the inferior vena cava **(IVC)** on the patient's right and the aorta **(AO)** descends just anterior to the vertebral body **(VER)** on the left. The spinal cord is visible within the spinal canal **(SC)** (from Crooks et al[2]).



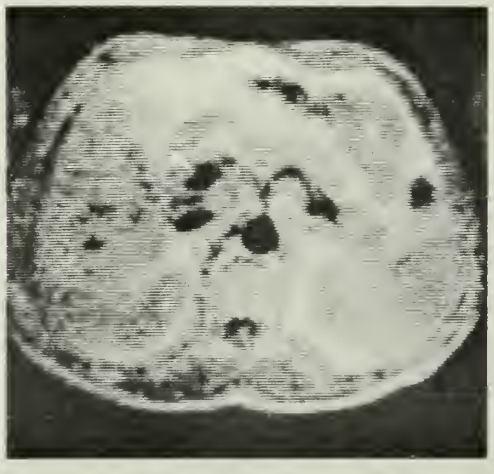


Figure 14.—Lymphoma: CT and MR imaging scans. The CT scan **(left)** shows adenopathy which is not visible with nuclear magnetic resonance. The MR image shows the celiac axis **(small arrow),** and the splenic and portal veins **(large arrows)** more distinctly (from Alfidi et al[12]).

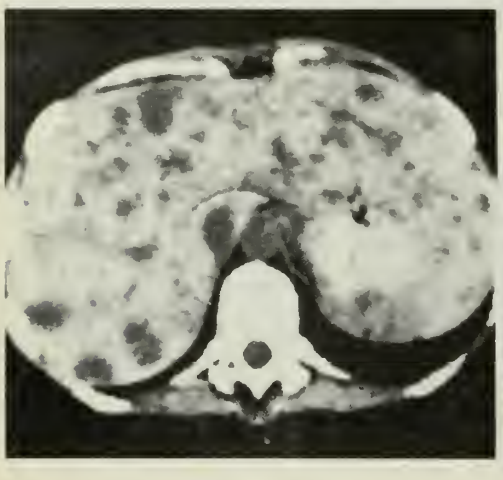


Figure 15.—Metastatic thyroid carcinoma: CT and inversion recovery scans. Small metastatic foci are visible in both images. The tissue contrast is greater in the MR imaging scan **(right)** (from Doyle et al[16]).

by a combination of body surface coils to apply the radio-frequency pulses and a method called topical magnetic resonance (TMR). Coils a few centimeters in diameter applied to the skin can produce high frequency radio pulses that are capable of penetrating several centimeters into the body. The tissue volume irradiated by the pulse is disc-shaped with a diameter roughly equal to the coil diameter and located about one coil diameter beneath the skin surface. This rather large volume is then limited by the use of TMR, in which the main magnetic field is focused within a more limited volume in the region of tissue irradiated by the surface coil. The volume of interest defined by the TMR can be moved around within the sensitive

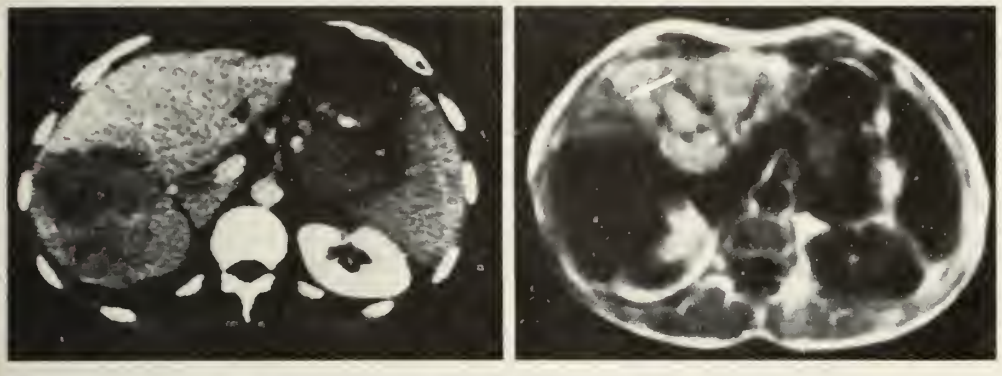


Figure 16.—Hepatoma: Contrast-enhanced CT and inversion recovery scans. The hepatoma is clearly visible in both images, although the MR images offer greater contrast **(right).** The MR imaging scan also shows a wedge-shaped area of infarction **(arrow)** just anterior to the tumor; this area is not visible in the CT image (from Doyle et al[16]).

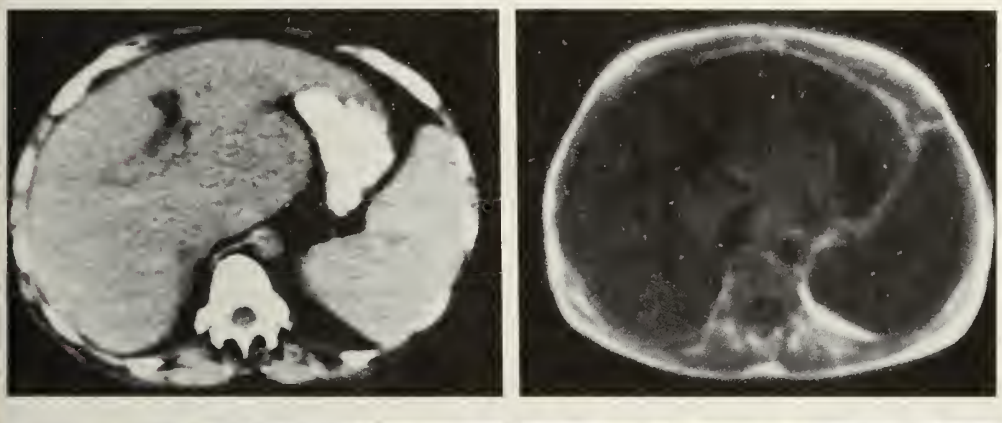


Figure 17.—Cirrhosis: CT and inversion recovery scans. The CT scan shows liver enlargement **(left).** In the MR image **(right)** the liver is diffusely abnormal and dark because of prolonged T_1 (from Doyle et al[16]).

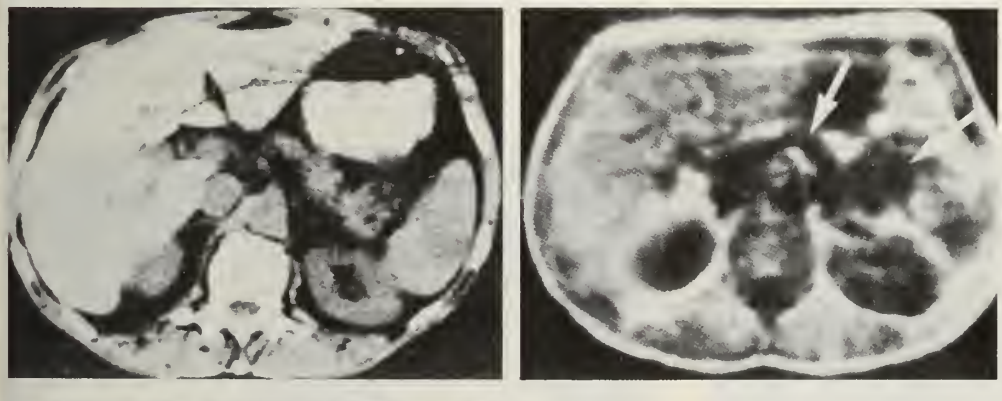


Figure 18.—Pancreatitis: CT and inversion recovery scans. The body and tail of the pancreas appear irregular in the CT scan **(left).** In the MR imaging scans they appear dark because of increased T_1 **(arrows)** (from Young et al[19]).

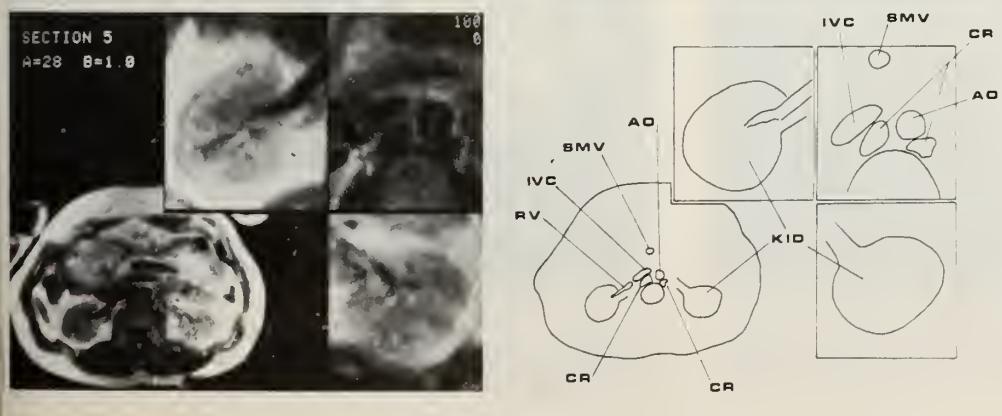


Figure 19.—Normal kidney: Spin-echo scan. The renal cortex, medulla and renal vein **(RV)** are all clearly seen in the normal and enlarged MR images. Also visible are the aorta **(AO)** , superior mesenteric vein **(SMV)**, inferior vena cava **(IVC)** and diaphragmatic crura **(CR)** (from Crooks et al[2]).

region under the coil. To date, tissue regions as small as 6 cm in diameter have been examined spectroscopically in humans.

Because of chemical shifts, the resonance frequencies from the phosphorus in phosphocreatine, adenosine triphosphate (ATP) and inorganic phosphate are all slightly different (Figures 20, 21). Even the resonance from ATP phosphorus is split into three peaks. The areas under the peaks provide a measure of the relative concentrations of phosphorus in different chemical configurations. The relative concentrations of ATP and phosphocreatine reflect the local tissue oxygen tension because ATP is regenerated from phosphocreatine by aerobic metabolism. The signal from inorganic phosphate depends on the pH of the sample and has two peaks which reflect intra- and extracellular pH. Recent studies of the myocardium[23] of animals and of the human forearm[24] have shown that ischemia produces changes in the phosphorous magnetic resonance spectrum of these tissues within minutes. These changes reflect the shift of ATP towards phosphocreatine and the decrease of intracellular pH due to lactate production. They occur well before any edema or structural change. Other

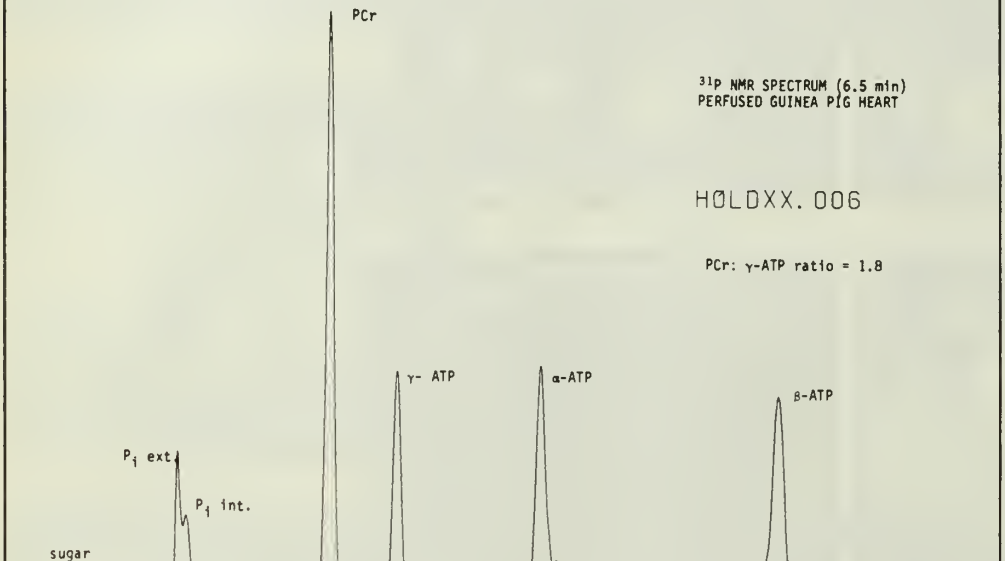


Figure 20.—^{31}P nuclear magnetic resonance spectrum of a perfused guinea pig heart. Separate peaks are visible for adenosine triphosphate (ATP), phosphocreatine (PCr), intracellular and extracellular inorganic phosphate and sugar phosphate. This high-resolution spectrum gives information about the amount of ATP relative to phosphocreatine (related to tissue oxygen tension) and the intracellular and extracellular pH (indicator of lactate production) (from Nunnally[22]).

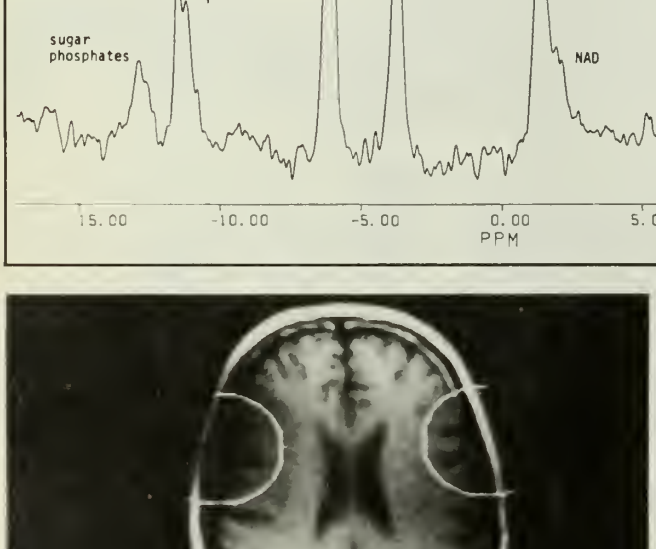


Figure 21.—Phosphorus spectrum from a normal brain. This is the first spectrum obtained on an MR imaging unit also capable of human whole body imaging (reproduced with permission of General Electric Co, copyright 1983).

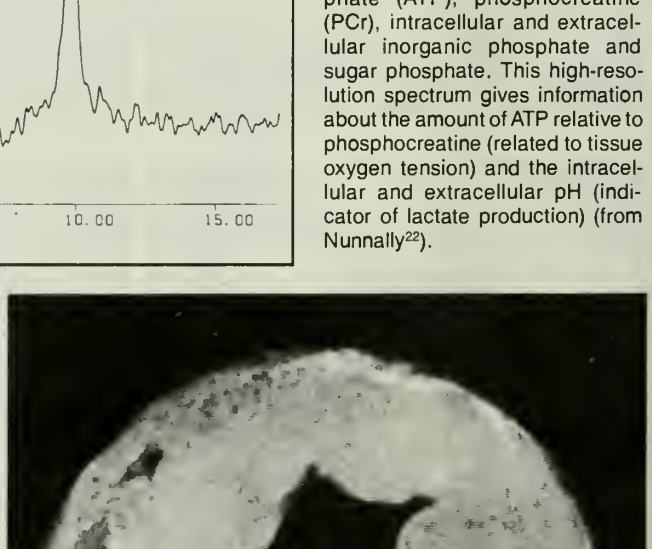


Figure 22.—Surgically induced infarction in a canine heart: MR imaging scan after intravenous administration of manganese. The normal area is white from manganese in the blood. The infarcted area is dark because it is not perfused (from Goldman et al[33]).

studies have shown that measuring the intracellular pH of a kidney before transplant helps to predict its survival in a new host, because a higher intracellular pH implies that there is relatively little ischemic damage.[25] The same investigators have shown that increased buffering capacity in the solution used to flush the donor's kidney improves its chances of survival.[25] Pretreatment with verapamil and chlorpromazine preserves ATP in the ischemic zone of perfused rabbit heart.[26] It has also been shown that the muscles of patients with Duchenne's dystrophy have no glycerol-3-phosphate and less total phosphorus, although cases that are not hereditary also have no glycerol-3-phosphate, but have normal amounts of total phosphorus.[27] These findings suggest that phosphorous magnetic resonance studies will aid in the investigation of mechanisms of a variety of diseases, in assessment of the effectiveness of current treatment methods and in the development of more effective therapy.

Much of the current knowledge of metabolic pathways has come from studies using carbon 14 as a radioactive tracer. About 1% of carbon in the body is carbon 13 and this isotope yields an MR imaging signal. Spectra from carbon 13 are more complicated than many others because its resonance is affected by both chemical shifts and an effect called proton-carbon spin coupling. Spin coupling arises because electrons are affected by proton resonance and transfer this influence to carbon nuclei, splitting the carbon signal into several components. Special techniques are required to minimize spin coupling in the magnetic resonance analysis of carbon 13.

The carbon 13 signal can be made stronger by using a carbon 13-enriched diet to enhance concentration of carbon 13 in the body. This approach is expensive, but still less costly than many carbon 14 experiments.

When carbon 14 is used, the animal must be sacrificed at a specific time, the organs of interest removed and the compounds extracted, separated and measured to yield a profile of the metabolic state at the moment of sacrifice. Carbon 13 magnetic resonance permits the study of an intact system and the monitoring of a reaction sequentially through many stages along a pathway. For example, hepatocytes have been studied in vivo using carbon 13-labeled glucose, glycerol and alanine.[28,29] Progression of the carbon 13 label through different positions in the glucose molecule permits the determination of specific metabolic pathways.

The feasibility of making images reflecting the distribution of fluorine,[30] sodium[31] and phosphocreatine and ATP,[32] has recently been demonstrated. The spatial resolution of these images is far less than that of hydrogen, and the imaging times are much longer. Because inorganic phosphate levels increase and phosphocreatine levels decrease in ischemic heart muscle, separate images of the heart from the resonance signals of inorganic phosphate and phosphocreatine might show the presence of ischemic and infarcted areas. Breakdown of the sodium-potassium pump from ischemia allows sodium to diffuse from the bloodstream into damaged cells, leading to the possibility of sodium images of stroke. Sodium is plentiful in the serum and provides yet another way to image blood vessels. Fluorine resonance could be useful with fluorine-containing contrast agents or physiologically active tracers that are sequestered and metabolized by specific tissues.

Because of the presence of an unpaired electron, oxygen and manganese exhibit paramagnetism (that is, weak magnetic properties). The magnetism of these elements is about 1,000 times stronger than that of hydrogen. The presence of paramagnetic ions can significantly affect proton relaxation times. The feasibility of using a paramagnetic contrast agent to highlight differences between regions of perfused and nonperfused tissue is illustrated in Figure 22. It is not clear whether manganese will highlight the disruption of the blood-brain barrier and become for proton imaging of the brain what iodine is for CT. Oxygen is also interesting as a contrast agent because it is naturally present in the body. There is a stronger magnetic resonance signal from blood in the left ventricle and the myocardium when the patient breathes pure oxygen compared with room air. It may someday be possible to image a myocardial infarction simply by using an oxygen mask to highlight the diseased area. Other possibilities for magnetic resonance imaging contrast agents include chelated compounds with ferromagnetic and paramagnetic properties.

Conclusion

Economic factors will largely determine how soon MR imaging becomes widely used as an imaging tool. The cost of a scanner ($800,000 to $2.2 million) is high. Third-party reimbursement for MR imaging procedures is just becoming available at this time, and many hospitals currently cannot afford an MR imaging unit. By the time the reimbursement situation changes, much more will be known about the usefulness of MR imaging, primarily as a product of the experience gained from the use of scanners now being installed. Hospitals will then be in a better position to decide whether they want an MR imaging unit and what type is best for them.

The main applications of MR imaging in clinical medicine currently are proton imaging and biochemical analysis. At the moment, only proton imaging is used clinically, and the closest competitor to MR imaging is CT. Because medicine is familiar with how CT works and what it does, and because the price of an MR imaging unit is equal to, or somewhat higher than that of a new CT scanner, MR imaging must be proved superior in some areas if it is to become an important imaging modality. In many applications to the central nervous system, it already has an edge over CT because of its improved contrast sensitivity and its ability to make sagittal and coronal sections directly.

The uniqueness of MR imaging lies in its sensitivity to blood flow, ease of obtaining gated cardiac images and ability to detect changes in the relaxation variables of tissues before there is obvious structural change. These capabilities suggest that MR imaging will be important in the diagnosis and management of a variety of cardiovascular conditions and tumors; institutions specializing in these areas that are considering the purchase of an additional CT scanner might well consider the acquisition of an MR imaging unit instead. Unfortunately, widespread clinical trials of MR imagers are only just beginning, and there are not yet enough data to recommend MR imagers to most hospitals. This observation is especially true in light of growing pressures to contain the costs of medical care. No studies have yet been done to determine the cost effectiveness of MR imaging versus other modalities; this issue remains to be addressed in the near future.

Biochemical analysis of intact tissues by magnetic resonance was begun only a few years ago. To date, only labora-

tory animals and human limbs have been studied in any detail. The results are exciting and have established a place for magnetic resonance as a tool for research into normal metabolism, metabolic disorders and ischemia. The potential impact of spectroscopic magnetic resonance at the clinical level is great because of the sophisticated analysis it makes possible and because many of the more common diseases are relatively refractory to current treatments. It is conceivable that magnetic resonance ultimately will be able to define portions of diseased tissue that are salvageable, to identify the best surgical or medical treatment and to monitor its effectiveness. The latter is an area in which magnetic resonance could be unique.

MR imaging technology has exploded in the last few years. Few would have predicted how far it has come in so short a time. It is hard to predict now where it will be in a few years because there is so much potential, as well as so many unknowns. In all likelihood, MR imaging will have a place of significance in medicine and will be an exciting tool for many years to come.

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Specialty Conference

Recent Trends in the Management of Life-Threatening Ventricular Arrhythmias

Moderator
BRAMAH N. SINGH, MD, PhD

Discussants
JAMES N. WEISS, MD; KOONLAWEE NADEMANEE, MD; JOHN H. WITTIG, MD, *and*
PETER GUZY, MD, PhD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine, UCLA School of Medicine, Los Angeles. William M. Pardridge, MD, Associate Professor of Medicine, is Director of Conferences.

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Significant advances have recently been made in understanding the mechanisms and the rationale of therapy for ventricular arrhythmias responsible for sudden death. The mainstay of therapy remains pharmacologic but surgical intervention and implantable electronic devices hold considerable promise. Programmed electrical stimulation of the heart permits the electrophysiologic mechanism of the arrhythmia to be established in many instances; the suppression of the inducible arrhythmia by various classes of electrophysiologic agents may provide a reliable index for predicting long-term therapy. The pharmacologic suppression of complex ectopy is also predictive of long-term efficacy but its relation to the suppression of inducible arrhythmia is not defined. Particularly significant is the development of new antiarrhythmic agents such as amiodarone. Amiodarone lengthens cardiac repolarization and has a powerful suppressant effect on spontaneously occurring arrhythmias but less so on inducible ventricular tachycardia. It has a significant potential to prolong life in patients with life-threatening ventricular arrhythmias. Further advances in electropharmacology and surgical treatment of ventricular arrhythmias and in implantable devices are imminent.

BRAMAH N. SINGH, MD, PhD:* The treatment of life-threatening ventricular arrhythmias has recently undergone significant changes. The current therapeutic trends are beginning to assume an increasingly rational basis with a shift away from the essentially empirical approach that has dominated antiarrhythmic therapy for many decades. The newer advances that have contributed to this growing trend should reduce the mortality for patients with malignant ventricular tachyarrhythmias.[1] Electrophysiologic studies in isolated tissues and in intact animals have shown that most ventricular arrhythmias arise on the basis of reentry and less commonly on the basis of abnormal automaticity, spontaneous or triggered as a result of early or late afterdepolarizations.[2] However, the present diagnostic approaches still do not permit the unequivocal determination of the electrophysiologic mechanisms underlying the various forms of ventricular tachycardias. Programmed electrical stimulation of the heart in humans has, nevertheless, provided new insights into the potential mechanisms of ventricular tachyarrhythmias.[3] More important, the technique has proved of great value in the rational choice of antiarrhythmic agents, conventional and investigational, for controlling sustained ventricular arrhythmias.

Significant advances have also been made in other areas of arrhythmia diagnosis and quantitation. For example, compact Holter analog analysis has been valuable in determining the correlation between the genesis of ventricular arrhythmias and transient or protracted bouts of myocardial ischemia.[4] Furthermore, the role of ambulatory electrocardiographic (ECG) monitoring in the detection and quantitation of complex ventricular ectopy[5] for diagnosis and monitoring treatment of spontaneously occurring ventricular tachyarrhythmias has been substantiated.

Perhaps no less significant is the development of new therapeutic modalities for the control of life-threatening ventricular arrhythmias. First, a plethora of newer antiarrhythmic

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(Singh BN, Weiss JN, Nademanee K, et al: Recent trends in the management of life-threatening ventricular arrhythmias—Interdepartmental Conference, VA Wadsworth Medical Center and University of California, Los Angeles [Specialty Conference]. West J Med 1984 Nov; 141:649-665)

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiography
ERP = effective refractory period
PVC = premature ventricular contraction
VT/VF = ventricular tachycardia/ventricular fibrillation

compounds have been synthesized and electrophysiologically characterized and are undergoing clinical evaluation.[6] They hold considerable promise. Second, new surgical techniques aided by electrophysiologic mapping to eradicate the focus of origin or to interrupt reentry circuits of dysrhythmias have been developed and successfully used in certain subsets of patients. Finally, preliminary experience has suggested that mortality in selected patients may be curtailed by using automatic implantable defibrillators, which can identify and terminate ventricular arrhythmias in inpatients[8,9] and outpatients.[10]

In this conference we consider aspects of these various newer approaches to controlling life-threatening ventricular arrhythmias in relation to the fundamental and clinical electrophysiologic mechanisms of such dysrhythmias.

Cardiac Electrophysiology and the Genesis of Arrhythmias

JAMES N. WEISS, MD:* Regulation of the heartbeat is mediated by the cardiac action potential, a complex phasic electrophysiologic event caused by transient sequential changes in the permeability of the cell membrane to various ions. An action potential arising in the sinus node is transmitted in a highly synchronized manner throughout the myocardium, traversing tissues with heterogeneous electrophysiologic properties, which may change considerably and differently in response to external factors, such as autonomic tone or drugs. To understand the mechanisms that give rise to arrhythmias and how antiarrhythmic drugs may terminate or prevent them, some fundamental features of the cardiac action potential need to be understood.

The Cardiac Action Potential

Figure 1 shows two fundamental types of cardiac action potentials. The fast response is characterized by a resting membrane potential of -70 mV to -90 mV. When the membrane potential is raised by electrotonic current or spontaneous diastolic depolarization to threshold, a rapid upstroke due to the influx of sodium ions through the fast sodium channel occurs. This upstroke can be blocked by tetrodotoxin. Normal Purkinje fibers show the fast response and may exhibit spontaneous diastolic depolarization, which causes them to fire spontaneously. Normal atrial and ventricular myocardium has the fast response usually without diastolic depolarization. The slow response is characterized by a low resting potential (-40 mV to -60 mV) and a slow action-potential upstroke. The slow upstroke is due to an influx of primarily calcium ions through the slow channel and is blocked by verapamil and other calcium antagonists but not by tetrodotoxin. The slow response can also show diastolic depolarization, such as in the normal sinus node. The atrioventricular nodal cells show the slow response often with diastolic depolarization. Cells normally having a fast response (for example, ventricular myocardium) can develop the slow responses if they are partially depolarized by current, elevated extracellular potassium concentrations, drugs or ischemic damage. The distinction between fast and slow response is important because the action-potential upstroke velocity is a major determinant of conduction velocity in the myocardium. The reduced upstroke velocity due to slow response or attenuated fast response can result in depressed conduction through cardiac tissue, a key predisposing factor to the development of certain types of arrhythmias.

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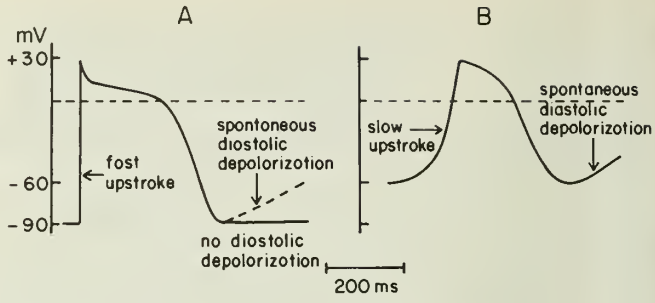

Figure 1.—Two types of cardiac action potentials. **A,** The fast response is characterized by a high resting potential and rapid upstroke. Spontaneous diastolic depolarization may occur in Purkinje fibers but not in normal atrial or ventricular myocardium. **B,** The slow response is characterized by a low resting potential and slow upstroke. Spontaneous diastolic depolarization may be present.

Another important concept with respect to arrhythmogenesis and the actions of antiarrhythmic drugs is refractoriness, particularly the indicator designated the *effective refractory period* (ERP). The ERP of cardiac tissue is defined as the period from the onset of the action potential to the time in the cardiac cycle when another action potential that can propagate can be elicited by an applied stimulus. Two types of changes in the ERP should be distinguished. The first is the so-called voltage-dependent change in which the myocardial fiber must repolarize to a certain minimum level of membrane potential before a second propagated action potential can be generated. Thus, shortening of the action-potential will reduce the ERP; the converse will occur with the lengthening of the action-potential duration. Alternatively, the ERP may be lengthened when there is a delay in the return of excitability independently of changes in repolarization (a time-dependent phenomenon). The ERP may outlast the entire duration of repolarization (postrepolarization refractoriness), an electrophysiologic property that is characteristic of slow-channel-dependent fibers, such as the atrioventricular node, and one that may be induced by inhibiting the fast sodium channel—that is, by local anesthetic type of antiarrhythmic drugs—in fast-response-dependent myocardial fibers. The differences between voltage and time-dependent mechanisms of alteration in the ERP (Figure 2) are significant in delineating the fundamental nature of cardiac arrhythmias and in interpreting the action of antiarrhythmic agents.[11]

Genesis of Ventricular Arrhythmias

The mechanism of ventricular arrhythmias, as in the case of other dysrhythmias, can be categorized into disorders of impulse formation (enhanced automaticity or triggered automaticity), disorders of impulse conduction (such as reentry) or combinations of both.[2] As will be discussed below, these electrophysiologic concepts have been validated reasonably

TABLE 1.—*Mechanisms of Arrhythmias and Their Probable Clinical Counterparts*

Mechanism of Arrhythmias	*Clinical Arrhythmias*
Automaticity	
Nontriggered	
Normal	Escape rhythm in complete heart block
Abnormal	?Noninducible ventricular tachycardia and supraventricular and ventricular ectopy
Oscillatory prepotentials	No clinical counterpart evident
Triggered Automaticity	
Early afterdepolarizations	?Ventricular tachycardia due to drug-induced QT prolongation (torsade de pointes)
Delayed afterdepolarizations	Ventricular tachycardia due to digitalis toxicity ?Mitral valve prolapse arrhythmias
Reentry	
Ordered reentry	Most inducible ventricular tachycardia, supraventricular tachycardia in Wolff-Parkinson-White syndrome and atrioventricular nodal tachycardia; also probably supraventricular and ventricular ectopy
Random reentry	Ventricular fibrillation, atrial fibrillation
Reflection	No clinical counterpart apparent

well in experimental models; their applicability to the clinical context is still essentially inferential[3] but the classification is still of clinical value. For example, clinically there are no electrophysiologic criteria that unequivocally differentiate reentry from the various forms of automaticity, nor are there tools, such as pacemakers, drugs, cardioverters or surgical techniques, that exert specific enough effects to separate the two possibilities. Extracellular recordings of automatic activity, however, hold promise about the possibility of accurate differentiation in the future.[3] Table 1 summarizes the mechanisms of arrhythmogenesis delineated from experimental studies and shows their possible clinical correlates.

Nontriggered Automaticity

Arrhythmias due to nontriggered automaticity can result from the normal automaticity, abnormal automaticity or oscillatory prepotentials. The precise basis for such variations of automaticity is still not certain. Normal automaticity refers to diastolic depolarization occurring at high resting potentials (–70 mV to –90 mV) and propagating by a fast response. Abnormal automaticity refers to diastolic depolarization occurring at low resting potentials (–40 mV to –60 mV) and propagating by a slow response. This term may be somewhat misleading because, although this form of automaticity is abnormal for atrial, His-Purkinje and ventricular muscle, it is the normal mechanism of impulse formation in the sinus node. Both normal and abnormal automaticity occur spontaneously and are not dependent on preceding action potentials—that is, they are not inducible by programmed stimulation of the heart.

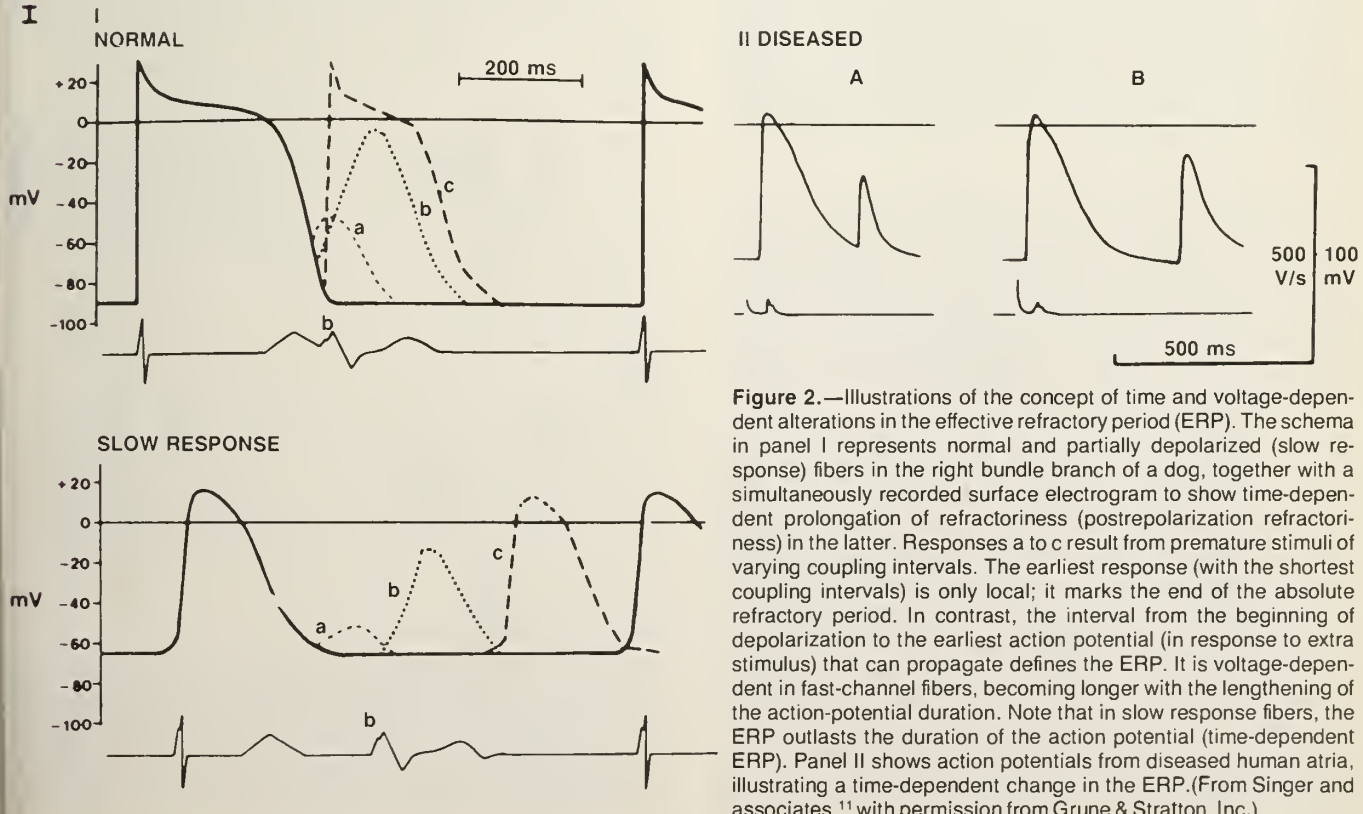

Figure 2.—Illustrations of the concept of time and voltage-dependent alterations in the effective refractory period (ERP). The schema in panel I represents normal and partially depolarized (slow response) fibers in the right bundle branch of a dog, together with a simultaneously recorded surface electrogram to show time-dependent prolongation of refractoriness (postrepolarization refractoriness) in the latter. Responses a to c result from premature stimuli of varying coupling intervals. The earliest response (with the shortest coupling intervals) is only local; it marks the end of the absolute refractory period. In contrast, the interval from the beginning of depolarization to the earliest action potential (in response to extra stimulus) that can propagate defines the ERP. It is voltage-dependent in fast-channel fibers, becoming longer with the lengthening of the action-potential duration. Note that in slow response fibers, the ERP outlasts the duration of the action potential (time-dependent ERP). Panel II shows action potentials from diseased human atria, illustrating a time-dependent change in the ERP.(From Singer and associates,[11] with permission from Grune & Stratton, Inc.)

Experimentally, certain techniques may be used to distinguish between these two forms of automaticity.[12] For example, overdrive pacing suppresses normal automaticity but not abnormal automaticity, whereas verapamil suppresses both. Moricizine (ethmozine), an experimental antiarrhythmic drug, more selectively suppresses abnormal automaticity. The role of normal and abnormal automaticity in human ventricular arrhythmias has not been established. Fascicular and idioventricular rhythms in the setting of complete infranodal heart block are examples of normal automaticity, but extremely rapid ventricular arrhythmias probably do not result from this mechanism. Normal automaticity has been seen in diseased human ventricular myocardium.[13] Abnormal automaticity usually occurs in subendocardial Purkinje fibers overlying an area of myocardial infarction in experimental animals[14,15] and in diseased human atrial and ventricular myocardium.[13,16-18] Abnormal automaticity is probably responsible for the high incidence of premature ventricular beats during the first 24 hours after myocardial infarction. In cases of chronic coronary artery disease, abnormal automaticity has been proposed to account for about 10% of patients with recurrent ventricular tachycardia in whom ventricular tachycardia cannot be induced by programmed stimulation of the heart. In patients with noncoronary artery disease, cardiomyopathy and recurrent ventricular tachycardia, the frequency of noninducible ventricular tachycardia is even higher. Parasystole may be the most common clinical manifestation of these forms of automaticity, in which depressed conduction in tissue surrounding the automatic focus protects the focus from being suppressed by sinus impulses (although the sinus impulses may modulate the behavior of the parasystolic focus). This phenomenon has recently been documented to occur in diseased human ventricular myocardium removed during a cardiac procedure.[13] Parasystole may also occur as a result of oscillatory prepotentials reaching the threshold in cardiac fibers (Figure 3), a third form of automaticity[19] whose role in clinical arrhythmias is unknown.

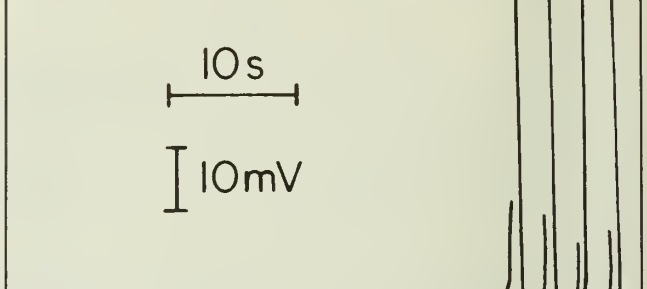

Figure 3.—Oscillatory prepotentials. These oscillations in membrane potential may reach their threshold and generate sustained rhythms.

Triggered Automaticity

The remaining mechanisms of arrhythmias (triggered automaticity and reentry) have one important common characteristic: they are dependent on preceding stimulation of the heart—that is, they can be induced (and usually terminated) by programmed stimulation of the heart both clinically and experimentally. Initially it was thought that the ability to initiate or terminate an arrhythmia by pacing implied that reentry was the mechanism. Subsequently, however, two forms of automaticity have been recognized that also show this property. Early or delayed afterdepolarizations may occur after a driven action potential (Figure 4). If the afterdepolarization reaches its threshold, it can generate a second action potential and the process may become self-sustaining. Early afterdepolarizations (Figure 4A) occur before the action potential has completely repolarized, generally in cells with a high resting potential. They have been found in Purkinje fibers under conditions of mechanical trauma, severe perturbation of the ionic environment and exposure to toxic concentrations of drugs that severely prolong the action-potential plateau, such as *N*-acetyl procainamide.[19,20] In the latter case, early afterdepolarizations were potentiated by slow pacing rates and suppressed at faster rates. Their role in human ventricular arrhythmias is unclear but it is tempting to speculate that ventricular tachycardia (torsade de pointes) in the setting of a long QT interval—particularly drug-induced—might involve this mechanism, because clinically this arrhythmia is also suppressed by increased heart rates. Delayed afterdepolarizations occur after the driven action potential has fully repolarized and are preceded by an afterhyperpolarization (Figure 4B). Sustained tachycardias from delayed afterdepolarizations can be induced and terminated

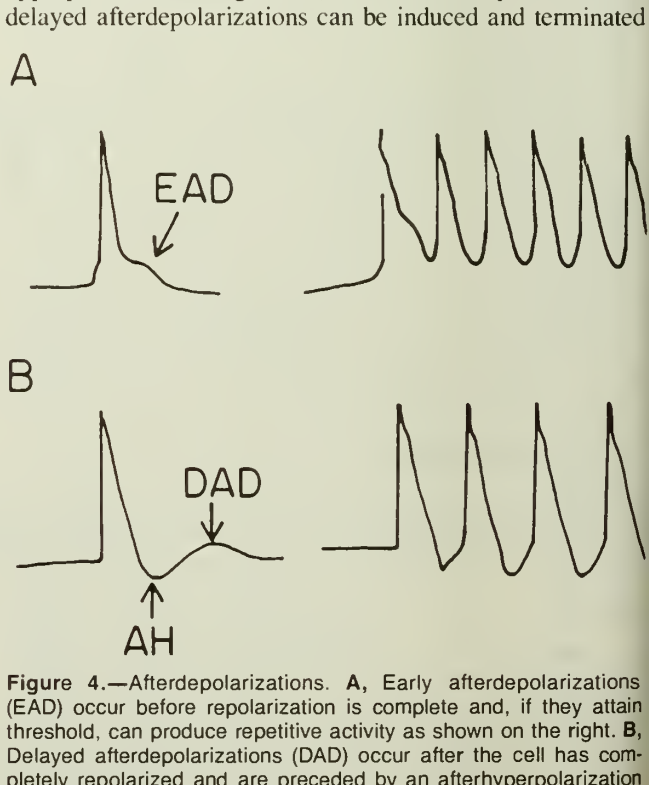

Figure 4.—Afterdepolarizations. **A,** Early afterdepolarizations (EAD) occur before repolarization is complete and, if they attain threshold, can produce repetitive activity as shown on the right. **B,** Delayed afterdepolarizations (DAD) occur after the cell has completely repolarized and are preceded by an afterhyperpolarization (AH). If the DAD reaches its threshold, repetitive activity may occur (shown at right).

by premature extrastimuli and are potentiated as the prematurity of the extrastimulus increases.[21] A major feature of this form of automaticity is that overdrive pacing may lead to acceleration of the tachycardia rate followed by termination (overdrive acceleration). Delayed afterdepolarizations can be induced in cells with a high or low resting potential by exposure to catecholamines (in fibers from the coronary sinus, anterior leaflet of the mitral valve and Purkinje system of experimental animals), by severe alterations in the ionic environment or by exposure to toxic concentrations of cardiac glycosides. Depending on how they were induced, delayed afterdepolarizations may be suppressed by verapamil, tetrodotoxin or lidocaine hydrochloride. Recently this form of automaticity has been documented in human myocardium.[13,18] Delayed afterdepolarizations causing repetitive activity were seen in diseased ventricular myocardium surgically removed from patients with recurrent ventricular tachycardia. Similar findings were reported in diseased atrial tissue from a patient with paroxysmal atrial tachycardia.[12,22]

Despite these intriguing correlations, the role of this form of triggered automaticity in human arrhythmias has not been conclusively established. Ventricular arrhythmias in cases of digitalis toxicity are probably due to this mechanism, and it has been postulated that supraventricular arrhythmias associated with the mitral valve prolapse syndrome might result from triggered automaticity in fibers from the mitral leaflet.[23] The phenomenon of overdrive acceleration, believed to be unique to this form of automaticity, is not uncommonly observed in cases of arrhythmia during programmed stimulation of the heart.[24]

Reentry

The most common mechanism responsible for human ventricular arrhythmias is reentry (Figure 5A). For reentry to occur, two conditions are necessary: unidirectional conduction block and slow conduction. If two pathways in the heart have disparate refractory periods, then an appropriately timed impulse will conduct through the pathway with the shorter refractory period but fail to conduct through the other pathway (unidirectional conduction block). If conduction through the first pathway is slow enough, the other pathway may have time to regain its excitability and conduct the impulse so that it can reenter the first pathway. The relation between refractoriness and conduction velocity is of critical importance in permitting the impulse to sustain its circus movement. Many antiarrhythmic drugs disturb this relation by altering the electrophysiologic properties that determine refractoriness and conduction velocity. A properly timed external impulse can also terminate the reentrant arrhythmia by simultaneously blocking both pathways of the circuit (Figure 5). These principles form the basis for studying clinical arrhythmias during a cardiac electrophysiologic study (see below). The slow response action potential (Figure 1B), or an attenuated fast response potential with slow conduction, may predispose ventricular myocardium to the development of reentry. The slow response has been documented to occur in diseased human ventricular tissue surgically removed from patients with recurrent ventricular tachycardia.[13,18] Recently it has been shown that under certain conditions the fast response can also be associated with slow conduction predisposing to reentry.[25]

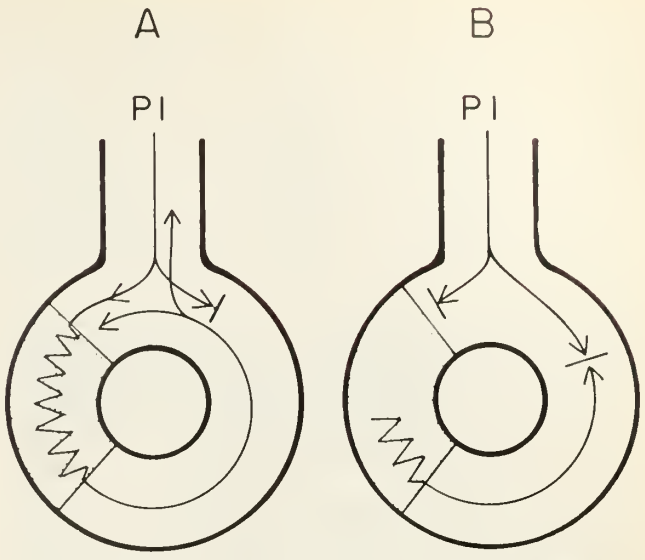

Figure 5.—Schema of reentry. **A,** Conduction of a premature impulse (PI) is blocked in one direction but conducts slowly (indicated by sawtoothed line) in the other. The slow conduction through one pathway permits the other pathway to regain excitability so that the impulse can reenter the loop. **B,** Termination of reentry by a premature impulse. The PI arrives too early to be conducted through the slow region (stippled area) and collides with the reentry impulse in the other pathway.

In experimental studies three major types of reentry have been described:

1. *Ordered reentry* occurs when the anatomic pathway of the reentrant circuit is relatively fixed. The classic example of ordered reentry in human arrhythmia where the reentrant circuit is well defined is circus-movement tachycardia in cases of the Wolff-Parkinson-White syndrome. Except for bundle branch reentry,[2] in which at least part of the reentrant circuit may be defined, the reentry circuits in ventricular tachycardia are difficult to establish with certainty. Most cases of recurrent ventricular tachycardia (in which the QRS morphology is unchanging) have been assumed to be due to ordered reentry in a diseased portion of the ventricular myocardium. Two lines of evidence tend to support this. First, most recurrent ventricular tachycardia can be initiated and terminated by programmed stimulation of the heart, which excludes nontriggered automaticity as the mechanism. Second, in several patients with recurrent ventricular tachycardia, intracardiac recordings have detected continuous electrical activity at sites believed to be near the origin of the tachycardia, which is present during tachycardia but not during sinus rhythm (Figure 6).[26] The intracardiac electrode detects electrical activity from many cells within a certain distance of its tip. If the total reentry circuit is located within this distance, electrical activity would be continuously detected throughout systole and diastole by the electrode during tachycardia but not during sinus rhythm. Because of artifacts, other investigators have questioned the reliability of this finding.[27]

2. *Random reentry* occurs when the anatomic pathway of the reentering impulse constantly shifts. It is characterized by an impulse that chaotically turns in and out on itself, its path

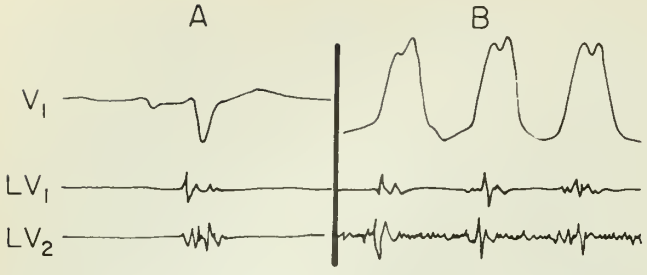

Figure 6.—Continuous electrical activity during ventricular tachycardia (VT). Electrocardiographic lead V_1 and two intracardiac leads positioned in the left ventricle (LV_1 and LV_2) are shown. **A,** During sinus rhythm, no electrical activity is detected at either intracardiac site during diastole. **B,** During VT continuous electrical activity is detected throughout systole and diastole at site 2, but not site 1, indicating that site 2 is near the reentry circuit causing VT.

being determined by constantly shifting boundaries of refractory tissues. Atrial and ventricular fibrillations are thought to be examples of random reentry. Unlike ordered reentry, random reentry can be induced in completely normal myocardium by extremely rapid pacing or delivering critically timed extrastimuli at high currents. A critical minimum mass of tissue is necessary to induce fibrillation in most myocardial tissue, supporting the hypothesis that fibrillation is due to reentry. In aggregates of cultured myocytes, however, electrical activity resembling fibrillation has been due to automaticity.[28]

3. *Reflection* differs from the other types of reentry in that only a single pathway is necessary to generate reentry. Figure 7 shows that if a strip of myocardium has a depressed segment, an impulse entering this segment may conduct slowly enough so that by the time it reaches normal tissue again (at A), the normal tissue at B has regained excitability. If excitation at A causes an electrotonic depolarization at B large enough to reach its threshold, a "reflected" action potential is generated. Reflection can be shown in Purkinje fibers and ventricular myocardium by artificially depressing a central

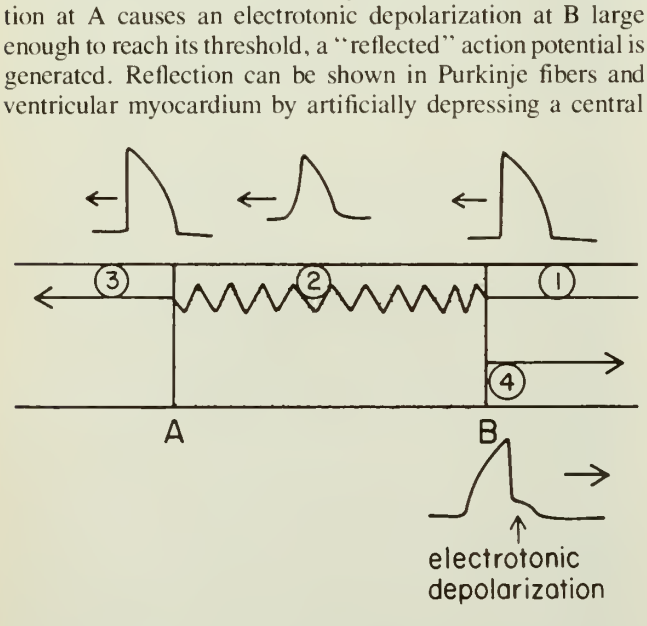

Figure 7.—Reflection. In a strip of cardiac tissue with a central zone (AB) of depressed conduction, an impulse (1) reaching point B is conducted slowly through the depressed area (2) and emerges at point A (3). Excitation at point A causes electrotonic current at point B to raise the local membrane potential to threshold and stimulate a "reflected" action potential (4). Representative action potentials are shown for each step 1 through 4.

segment of tissue[29]; whether or not reflection contributes to clinical arrhythmia has not been established.

In the preceding discussion the major mechanisms of tachyarrhythmia have been described. These have been identified in experimental studies and are believed to account for the common human arrhythmias observed clinically. In many cases specific clinical arrhythmias cannot yet be definitely attributed to a single mechanism. Through our expanding knowledge of the basic electrophysiology of arrhythmias, an increasingly rational approach to the treatment of these disorders using drugs, pacing techniques and surgical intervention can be devised.

Electrophysiologic Mechanisms of Antiarrhythmic Drugs

DR. SINGH: For the control of malignant ventricular arrhythmias, the pharmacologic approach still has the widest appeal, applicability and scope, despite the fact that a single ideal antiarrhythmic agent remains to be developed. For the rational pharmacologic basis for the treatment of arrhythmias to be established, not only does the nature of cardiac arrhythmia need to be understood, but also the fundamental mechanism of action of antiarrhythmic agents needs to be defined. In this regard, conventional and newer compounds can now be divided electrophysiologically into four discrete classes[30,31] on the basis of whether they inhibit the fast response in cardiac muscle (I), decrease sympathetic excitation to the heart (II), homogeneously lengthen cardiac repolarization without altering depolarization (III) and inhibit or abolish the slow response (IV). The major compounds in various classes and subclasses of action are listed in Table 2.

Class I drugs depress the fast sodium current (fast response) in cardiac muscle, thereby lengthening the dependent effective refractory period; the resting membrane potential is unaffected but phase 4 is depressed while the effect on repolarization is variable. For example, in the case of some drugs (now designated as class IA, such as quinidine, procainamide hydrochloride and disopyramide phosphate) the pronounced reduction in the fast response (or the fast sodium current) is associated (in an independent way) with a modest lengthening of the action potential (or QTc interval), a property that may be both beneficial and deleterious under different conditions. For example, in atrial flutter and fibrillation, lengthening of the atrial action potential by these agents may contribute to their tendency to restore and maintain sinus rhythm. In ventricular myocardium the lengthening of the QTc interval in conjunction with a greatly reduced conduction velocity may give rise to atypical ventricular tachycardia (torsade de pointes) in excessive doses or when associated with hypokalemia or hypomagnesemia. In the case of some class I agents, the duration of the action potential may actually become shorter. With these agents (designated as class IB and typified by lidocaine, mexiletine, tocainide, phenytoin, aprindine hydrochloride and possibly propafenone, pirmenol hydrochloride and moricizine), the net effect on the ERP is a balance between the time-dependent increase due to the inhibition of the fast channel and the *decrease* due to abbreviation of the time course of repolarization. Recently, another discrete subcategory (designated IC) of class I agents has become available;

TABLE 2.—*Comparative Mechanisms of Action of Antiarrhythmic Agents*

Class I	*Class II*	*Class III*	*Class IV*
A. Quinidine Procainamide hydrochloride Disopyramide phosphate	A. Propranolol hydrochloride Oxprenolol hydrochloride Alprenolol hydrochloride Pindolol Timolol maleate Nadolol Acebutolol Atenolol	Sotalol hydrochloride* Amiodarone Bretylium tosylate Clofilium phosphate *N*-Acetyl procainamide Melperone	A. Verapamil Diltiazem hydrochloride (Nifedipine)† Tiapamil Gallopamil (D-600)
B. Lidocaine hydrochloride Mexiletine Tocainide Aprindine hydrochloride Moricizine (ethmozine) Phenytoin Propafenone Pirmenol hydrochloride	B. Sotalol*		B. Bepridil hydrochloride
C. Flecainide acetate Encainide hydrochloride Cibenzoline Indecainide Lorcainide hydrochloride			

*Sotalol differs from other β-antagonists in lengthening cardiac repolarization. Also note that bepridil is a calcium-antagonist that differs from other members of the class in depressing fast channel activity.

†Nifedipine has no direct antiarrhythmic actions.

these agents greatly depress conduction in all parts of the heart, and some of them also have a potent suppressant action on premature ventricular contractions (''PVC killers''). The most prominent compounds in this category are flecainide acetate, encainide hydrochloride (and its metabolites), lorcainide hydrochloride and cibenzoline. Another feature that these compounds share is the differential effect that they have on repolarization in ventricular muscle and in Purkinje fibers, lengthening it in the former and shortening it in the latter. Significant arrhythmogenic potential of some of these compounds may relate not only to their pronounced depressant effect on conduction but also on the disparity in their actions on cardiac repolarization providing the substrate for focal re-excitation.

Some general features of class I agents relative to their value in controlling ventricular tachyarrhythmias should be emphasized. Because these drugs lengthen the ERP and depress the tendency to spontaneous depolarization, they have a wide spectrum of antiarrhythmic action, being effective in arrhythmias due to reentry and in those caused by enhanced automaticity. A feature of class I agents, which has also emerged recently from clinical studies, is that, as a class, the long-term efficacy of these compounds in controlling ventricular tachyarrhythmias may be predictable on the basis of their ability to prevent the reinduction of ventricular arrhythmias by programmed electrical stimulation of the heart in a clinical electrophysiology laboratory.[32] These observations suggest that these compounds alter the substrates required for reentry in patients with organic cardiac disease.

The class II agents, particularly the β-adrenoceptor-blocking drugs, reduce sympathetic excitation of the heart. The antiarrhythmic spectrum of these drugs is virtually identical despite the somewhat varying pharmacologic properties in terms of their potencies as local anesthetics, as partial agonists and as cardioselective or nonselective agents.[34] Their only electrophysiologic action of clinical relevance is the fact that all block phase 4 depolarization, especially that augmented by endogenous or exogenous catecholamines. We[33] have shown that the overall antiarrhythmic spectrum of action of β-blockers in cases of chronic ventricular arrhythmia will be narrow. Indeed, the agents in this class have a low potency for suppressing premature ventricular contractions[34] and rarely are they prophylactically effective against life-threatening ventricular tachyarrhythmias.[35] There are, however, two exceptions: First, this class of agents is particularly effective in exercise-induced ventricular tachycardia that is thought to be due to triggered automaticity.[36] Second, β-blockade is the pharmacologic therapy of choice in the relatively rare syndrome of long QT interval with a propensity to recurrent ventricular tachycardia or fibrillation, an arrhythmia and ECG abnormality most likely due to asymmetric sympathetic stimulation of the heart.[37] As a class of cardioactive agents, however, β-blocking compounds have recently drawn much attention because of their propensity to reduce the incidence of sudden death in survivors of acute myocardial infarction.[38] This effect is related to the β-blocking property of the compounds and seems to be mediated indirectly through amelioration of ischemia rather than a primary antiarrhythmic action.[39]

Perhaps one of the most significant observations in the past

ten years in the characterization of antiarrhythmic mechanisms has been that the uniform lengthening of the action-potential duration has a potent effect in preventing the development of arrhythmia.[6,40,41] This has been suggested by the alterations in the duration of repolarization of intracellularly recorded action potentials in hyperthyroid and hypothyroid atria.[42,43] It is also indicated by the striking effect of the drug amiodarone in prolonging the absolute refractory period in cardiac muscle[41] with little effect on the upstroke velocity of phase 0 of the transmembrane action potential (see below). This effect is also shown by bretylium tosylate during administration for an acute condition, myocardial ischemia,[6] and by amiodarone after protracted therapy.[41] Such an effect has been considered to be a distinct mechanism (class III) for terminating resistant ventricular arrhythmias. Several agents that seem to act predominantly by lengthening the action-potential duration (with the consequent prolongation of the ERP) are currently under study: sotalol hydrochloride, amiodarone, clofilium phosphate and *N*-acetyl procainamide. Other compounds that may also show, at least in part, the so-called class III activity are bepridil hydrochloride[44] and melperone.[45] Recent evidence shows that certain class III agents—such as amiodarone and sotalol—while being broad-spectrum antiarrhythmic compounds, may emerge as the most significant agents for the control of life-threatening ventricular arrhythmias. They seem to be effective in arrhythmias due to reentry and enhanced automaticity. However, their role in ventricular arrhythmias due to triggered automaticity—exercise-induced or torsade de pointes—is not defined. One feature of the action of these compounds as a class merits emphasis: because of their selective effect on myocardial repolarization, they exert no intrinsic negative inotropic effect[46] and some may be frankly positively inotropic.[45] Thus, unlike other electrophysiologic classes of antiarrhythmic compounds, class III agents exert little or no myocardial depressant effect, even in patients with cardiac failure. They constitute, therefore, a significant advance in the control of life-threatening ventricular tachyarrhythmias because most of these occur in patients with severe cardiac disease.[47]

Finally, agents that selectively block the slow channel in the myocardium have been categorized as showing a class IV antiarrhythmic action.[31] Verapamil is a prototype; it has little effect on the upstroke velocity of phase 0: it accelerates phases 1 and 2 of repolarization and depresses phase 4, especially where it is slow-channel dependent (slow response). In humans, calcium antagonists have no significant effect on the effective refractory period of the ventricle or the His-Purkinje system. Thus, it is not surprising that these compounds as a class exert little or no direct antiarrhythmic effects in cases of ventricular tachyarrhythmia,[48] nor do they predictably suppress premature ventricular contractions in patients with cardiac disease.[49] On the other hand, calcium antagonists may exert a potent antiarrhythmic effect indirectly by controlling myocardial ischemia complicating coronary artery spasm[50] and may become prophylactic agents of choice in this particular context.[51]

Thus, in the prophylactic control of most malignant or life-threatening ventricular arrhythmias, neither β-blockers nor calcium antagonists have a major role. In the past, class I agents have dominated the pharmacologic therapy for such tachyarrhythmias. Recent studies,[50-55] especially with the drug amiodarone, have shown the role of class III agents to emerge as an effective alternative and the possibility that the judicious use of this category of compounds may make a significant inroad into the morbidity and mortality figures from life-threatening ventricular arrhythmias in patients with cardiac disease. Thus, a critical reappraisal of the role of various electrophysiologic classes of antiarrhythmic compounds in the prophylactic control of life-threatening ventricular tachyarrhythmias is timely.

Drug Therapy for Ventricular Arrhythmias

KOONLAWEE NADEMANEE, MD:* Pharmacologic suppression remains the mainstay of therapy for ventricular tachyarrhythmias,[1,6] despite recent advances in surgical techniques and implantable antitachycardia and antifibrillatory devices (see below). The pharmacologic approach is applicable to the entire spectrum of ventricular tachyarrhythmias from simple or complex premature ventricular contractions (PVCs) to ventricular fibrillation. Although the data are not conclusive, increasing evidence has tended to delineate those subsets of patients with ventricular tachyarrhythmias who need aggressive antiarrhythmic therapy. Recent reports[56-58] have clearly established the benign nature of ventricular tachyarrhythmias in patients with structurally normal hearts. Unless patients are severely symptomatic, no specific antiarrhythmic therapy in such patients is either indicated or justified. In contrast, patients having structural heart disease (especially coronary artery disease) with ventricular tachyarrhythmias can be categorized into somewhat overlapping subsets in all of whom successful therapy might reasonably be expected to enhance survival; the presence of ventricular dysrhythmias, symptomatic or nonsymptomatic, in such patients is associated with sudden arrhythmic deaths. These arrhythmias are, therefore, designated life-threatening or malignant and patients with such dysrhythmias are recognized to be at high risk for sudden death.[56,59-64] Three categories of patients are recognized. The first includes those patients with frequent and complex PVCs without sustained ventricular tachycardia. The second comprises patients with symptomatic or nonsymptomatic ventricular tachycardia without a history of previous cardiac arrest, and the final group consists of the survivors of out-of-hospital cardiac arrests due to ventricular tachycardia or fibrillation. These three groups of patients constitute a continuum representing a spectrum of severity in electrical instability of the myocardium.

Significance of Premature Ventricular Contractions in Patients With Cardiac Disease

There is strong evidence fortified by recent data from ambulatory ECG monitoring that in patients with cardiac disease (especially coronary artery disease), the frequency and complexity of PVCs constitute indicators of increased risk of sudden cardiac death.[56,59-61] The evidence is particularly compelling in patients with reduced ventricular function.[59] For example, Schulze and colleagues[65] found that although advanced grades of PVCs occurred essentially in those with left ventricular ejection fractions of less than 40%, sudden arrhythmic deaths occurred only in patients who also had advanced grades of PVCs. Moreover, Rub-

*Department of Medicine, UCLA School of Medicine.

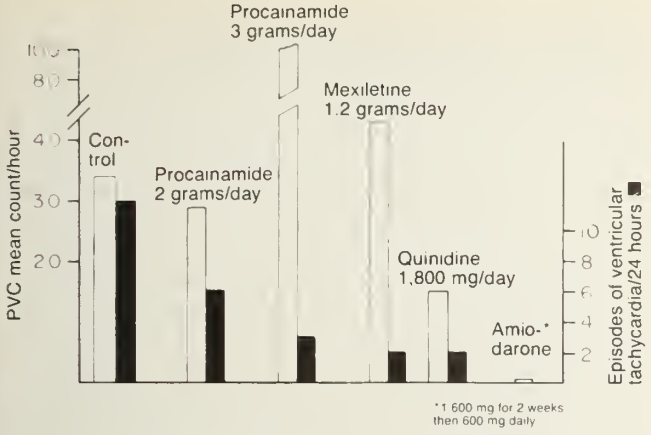

Figure 8.— Effect of various antiarrhythmic agents on total premature ventricular contraction (PVC) counts (ordinate on the left) and ventricular tachycardia beats (ordinate on the right) computed from 24-hour ambulatory electrocardiographic recordings. The goal of therapy is to eliminate ventricular tachycardia beats and, if possible, to reduce total PVC counts by more than 90%. In this patient, this goal was met only with the use of amiodarone (K. Nademanee, MD, and B. N. Singh, MD, PhD, unpublished observations, March 1982).

erman and associates[61] noted that patients with congestive heart failure who did not have advanced grades of PVCs showed a lower propensity for sudden cardiac death than those who had such arrhythmias but never had cardiac failure. These data provide a clear rationale for the pharmacologic suppression of advanced grades of PVCs in patients with cardiac disease and compromised ventricular function even in asymptomatic patients. To date, however, no systematic trial with antiarrhythmic compounds has unequivocally shown that either suppressing the total number of PVCs (by whatever percentage) or eliminating their complexity leads to enhanced survival in this subset of patients. Nevertheless, because of the established risk of sudden death due to PVCs and because of inferential evidence from patients with sustained (see below) ventricular tachycardia in whom eliminating advanced PVCs seems to prolong survival,[56] we feel aggressive attempts at eliminating complex PVCs and nonsustained runs of ventricular tachycardia are justified. Our approach is exemplified in Figure 8. The arrhythmias are verified and quantitated under control conditions by multiple ambulatory ECG recordings and serially on incremental dosing regimens of antiarrhythmic compounds under serum drug concentration control until the goal of therapy (without the development of side effects) has been met. As emphasized above, β-blockers and calcium antagonists have a low order of potency to suppress PVCs.

The precise potency profile for all conventional and investigational antiarrhythmic compounds is not available but the introduction of newer class I agents, such as encainide[66] and flecainide,[67] and class III agents such as amiodarone[68] indicates that not only a predictable PVC suppression may be attained by these agents but long-term controlled observations may permit the evaluation of prognostic significance of the PVCs. In a recent double-blind multicenter study[69] involving 280 patients with classic PVCs, 85% of patients given flecainide had 80% suppression of PVCs versus 57% of patients achieving the same suppression by quinidine. Furthermore, in 68% of patients flecainide produced a complete suppression of couplets and beats of ventricular tachycardia, whereas only 33% of the patients treated with quinidine had complete suppression. Figures for encainide are probably similar.[66] Although similar figures for procainamide and disopyramide are not available in this regard, they are unlikely to be different from those for quinidine. Our studies[68] and those of others[70] have shown that the drug amiodarone has the potency to reduce total PVC counts by more than 90% and to eliminate couplets and runs of ventricular tachycardia in more than 80% to 90% of all patients. Thus, antiarrhythmic compounds with a range of potency to suppress PVCs are now becoming available. For this reason, it is clearly important to establish by stringently controlled clinical trials whether PVC suppression is attended by a reduced incidence of sudden death in patients with cardiac disease.

Sustained Ventricular Tachycardia and Recurrent Cardiac Arrests

The subsets of patients with these two types of manifestations of ventricular tachyarrhythmias clearly represent those with the highest possible risk for sudden death. Such patients are in the greatest need of aggressive medical therapy; they also provide the widest scope and challenge for reducing mortality rates by the prophylactic control of recurrent arrhythmias. It is in these two subsets of patients that the use of all the newer modalities of treatment, such as investigational antiarrhythmic drugs,[66,71] surgical treatment of arrhythmias[72] and implantable electronic devices,[8-10] may lead to improved prognosis. Between 1930 and 1960, the six-month mortality in patients with ventricular tachycardia was between 50% and 80%, the mortality correlating with the severity of the underlying disease. A recent report from Stanford indicates an actuarial six-month mortality rate of 18 $\pm$ 3%.[73] Other studies, especially with survivors of out-of-hospital cardiac arrests, have shown a mortality figure between 30% and 50% in the first year.[60-64] Aggressive prophylactic therapy for such patients is clearly imperative. An appreciation of the clinical features of both subsets of these patients is relevant to the pharmacologic strategies necessary for the control of their ventricular tachyarrhythmias. In a variable number of patients with ventricular tachycardias and sudden death syndrome, a reversible cause can be identified and dealt with. This may range from electrolyte disturbances, arrhythmogenic drugs (including many antiarrhythmic compounds), episodic myocardial ischemia—such as that due to coronary artery spasm—to specific clinical situations in which a particular mode of therapy may be highly efficacious—such as β-blockade or left stellate ganglionectomy for the congenital long QTc-interval syndrome.[74] In most patients, however, the underlying cardiac disease is not reversible and continues to provide the substrate for reentry and enhanced automaticity[73]; the left ventricular ejection fraction is reduced,[68] often severely.[52]

From the standpoint of pharmacologic therapy, two features are worthy of emphasis. In survivors of sudden arrhythmic arrests, about 80% to 90% show frequent and often complex PVCs in serial 24-hour ambulatory ECG records[52,75]; in about 70% to 80% ventricular tachycardia or fibrillation is reproducibly inducible by programmed electrical stimulation of the heart.[52,76] In patients with symptom-

atic sustained ventricular tachycardia, PVCs are also present in about 80% to 90%,[68] whereas inducible ventricular tachycardia/ventricular fibrillation (VT/VF) may be elicitable in the 90% of patients.[32,73,77,78] Thus, in only a small fraction of patients, ambulatory ECG monitoring and programmed electrical stimulation fail to document the presence of electrical instability of the myocardium. These observations have therefore provided the basis for developing antiarrhythmic drug therapy for life-threatening ventricular arrhythmias.

Selection of Antiarrhythmic Drugs: Suppression of Spontaneous Versus Inducible VT/VF as Prognostic Indices

In selecting effective drug regimens for the control of life-threatening ventricular arrhythmias, three discrete approaches have been promulgated. The first was suggested by the work of Myerburg and co-workers,[75,79] who reported that procainamide or quinidine, given in doses to achieve and maintain therapeutic plasma concentrations, prevented VT/VF in all six patients, whereas VT/VF recurred in eight of ten patients in whom plasma drug concentrations were unstable and generally below the therapeutic range. Their data showed a dissociation between the suppression of PVCs and prevention of VT/VF and suggested the maintenance of the so-called therapeutic plasma drug values as a means to avert recurrent cardiac arrest. However, the number of patients in this study was small, the pretreatment analysis of arrhythmias was lacking and there was no control group. The second approach is the one indicated by the data reported by Graboys and colleagues.[56] They showed that eliminating complex ventricular ectopy (Lown, grades 4 and 5) by antiarrhythmic agents in patients with malignant ventricular arrhythmias (including those surviving cardiac arrest) led to a reduction in the incidence of sudden death. For example, of 123 such patients treated by individualized antiarrhythmic drug regimens and studied for 29.6 months, 35 patients died (11.2% annual mortality), of whom 23 died suddenly (8.2% annual mortality). Among 98 of these patients in whom antiarrhythmic drugs eliminated advanced grades of PVCs, only six deaths occurred (an annual death rate of 2.3%). In contrast, of the 25 patients in whom advanced PVCs were not controlled, 17 died. Various antiarrhythmic agents were used in the study and the most significant determinant of prognosis was simply the suppression of complex ventricular ectopy.

Finally, the method of drug selection that has attracted most attention recently is one in which the suppression of inducible VT/VF during acute drug testing has been found to predict the long-term outcome during long-term prophylactic therapy.[32,78,80] Numerous investigators have found that if VT/VF induced by programmed electrical stimulation can be suppressed by antiarrhythmic compounds at drug concentrations that subsequently can be attained during prolonged oral therapy using class I agents,[32,78,80] long-term arrhythmia control is highly predictable. Conversely, it has been found that the inability to identify an effective drug regimen during programmed electrical stimulation is predictive of a poor clinical outcome,[32,73,81] again when class I agents are used. The technique is clearly promising but it is not universally applicable, nor has it been fully validated or proved unequivocally reliable. For example, of the 31 patients reported by Ruskin and associates[81] to survive sudden out-of-hospital cardiac arrest, VT/VF was not inducible in six of the patients. In six others, acute drug testing failed to identify an effective regimen—that is, in about 40% the technique was not helpful. In the remaining 19 patients treated (9 with mexiletine only, 5 with quinidine only, 2 with a combination regimen, 3 with amiodarone) on the basis of the suppression of inducible VT/VF, there were no deaths during a mean follow-up of 15 months. Morady and associates, however, in a study of 45 patients who died suddenly,[76] found inducible ventricular tachycardia in 34 patients (76%); drug testing using conventional (class I) drugs showed suppression of inducible ventricular tachycardia in 9 of 34 patients (26%). Three of these nine patients (33%) had recurrent ventricular tachycardia or sudden death during a mean follow-up period of 20 months while receiving long-term therapy instituted on the basis of the induction studies.

The reasons for the differences between the data reported by Ruskin and co-workers[81] and those by Morady and associates[76] are not certain but they emphasize the need for further critical evaluation of the technique of invasive electrophysiologic studies in this regard before it can be promulgated unreservedly as a reliable method for the design of ongoing antiarrhythmic therapy in patients with malignant ventricular tachyarrhythmias. Furthermore, although the method is here to stay, at present it is not entirely certain whether it is indeed superior to that involving the suppression of spontaneously occurring ventricular arrhythmias documented on ambulatory ECG recordings. A stringently controlled study comparing the clinical utility of both techniques *in the same study* is still wanting. Furthermore, the two approaches are *not* mutually exclusive and, though the invasive nature of programmed electrical stimulation cannot be ignored, it is of much value not only for establishing the precise diagnosis of a wide QRS-complex tachycardia but also for establishing the appropriate therapy when other methods may not be applicable. Electrode catheter arrhythmia induction is, of course, an integral adjunctive resource for surgical treatment of arrhythmia.

Control of VT/VF by Lengthening Cardiac Repolarization

As indicated above, the so-called class III action is typified by the properties of the drug amiodarone, the best studied compound in this regard.[52-55] The compound also has a remarkable potency[68] for suppressing PVCs in a predictable manner.[52] To test the significance of PVC suppression versus inhibition of inducible VT/VF by programmed electrical stimulation, we have systematically (but not by blinded protocol) evaluated the drug's effect using optimal dosage schedules[52,68] in two independent series of patients. In the first,[68] 96 patients with life-threatening ventricular arrhythmias *refractory to two or more conventional agents* were treated with amiodarone and studied for 6 to 40 months (mean, 15 months). At the time of analysis, 75 patients were alive and well, with 7 patients dying from nonarrhythmic causes and 5 from arrhythmias. Nonfatal arrhythmias recurred in four patients, one early and three with late onset, and intolerable side effects occurred in five patients. In 72 of 96 patients, 24-hour Holter recordings were done before amiodarone therapy was administered; 63 (87.5%) showed frequent PVCs with complex forms and runs of ventricular tachycardia while not re-

ceiving specific antiarrhythmic therapy. The effects of amiodarone, documented by serial Holter recordings, are shown in Figure 9. Amiodarone, after the initial loading dose and at different periods of maintenance therapy, eliminated runs of ventricular tachycardia and reduced the total of premature ventricular contractions by 90% or more in 59 (93.7%) of 63 patients. In 43 such patients, arrhythmia induction by programmed electrical stimulation could be undertaken before and in 30 patients during steady-state drug therapy. In 14 of 30 patients VT/VF could still be reinduced by programmed electrical stimulation during drug therapy despite excellent clinical results. Indeed, with respect to the clinical outcome, the degree of suppression of spontaneously occurring arrhythmias found on Holter recordings and the magnitude of the increase in the ventricular ERP, the subset of 14 patients in whom VT/VF was reinducible during amiodarone therapy was indistinguishable from that of the 16 patients in whom it was not reinduced by programmed electrical stimulation during drug therapy despite excellent clinical results.

The results of these studies were concordant with our data in 40 consecutive patients surviving out-of-hospital cardiac arrests, and in whom conventional drugs were either not effective or not tolerated.[52] The mean ejection fraction for the group was 0.29 ± 0.12. The flow diagram in Figure 10 shows the clinical outcome of the 40 patients treated prophylactically with amiodarone. During the long-term administration of therapy the recurrence rate was low. This is further corroborated by determining the influence of amiodarone on the occurrence of VT/VF and survival analyzed by the life-table method. In 22 patients, data with respect to recurrent VT/VF before amiodarone therapy and during continuous amiodarone treatment were available. Figure 11 shows such an analysis for the significance of the difference of the occurrence of VT/VF during a 15-month period of observation. A significant difference ($P < .0005$) was found between the frequency of the recurrence of arrhythmias before and during amiodarone therapy. In Figure 12 the percentage of patients who remained free of VT/VF while taking amiodarone (upper panel) is presented. The recurrence rate of VT/VF and the total mortality (including four deaths not from arrhythmia) was low during the 24-month period of observation. The total annual mortality was less than 10%; the arrhythmic mortality was less than 5%, a figure that is concordant with data from another recent study.[76] In this study, however, the outcome was not studied relative to the suppression of spontaneous versus inducible VT/VF.

In 34 of our 40 patients, 24-hour Holter recordings could be done while all antiarrhythmic therapy was discontinued and before the amiodarone regimen was started. In all, 29 patients (85%) showed frequent runs of PVCs and one or more episodes of ventricular tachycardia—three or more consecutive runs of PVCs at a rate of more than 100 beats a minute. In five patients there were no runs of ventricular tachycardia beats. In all 29 patients in whom control 24-hour Holter recordings

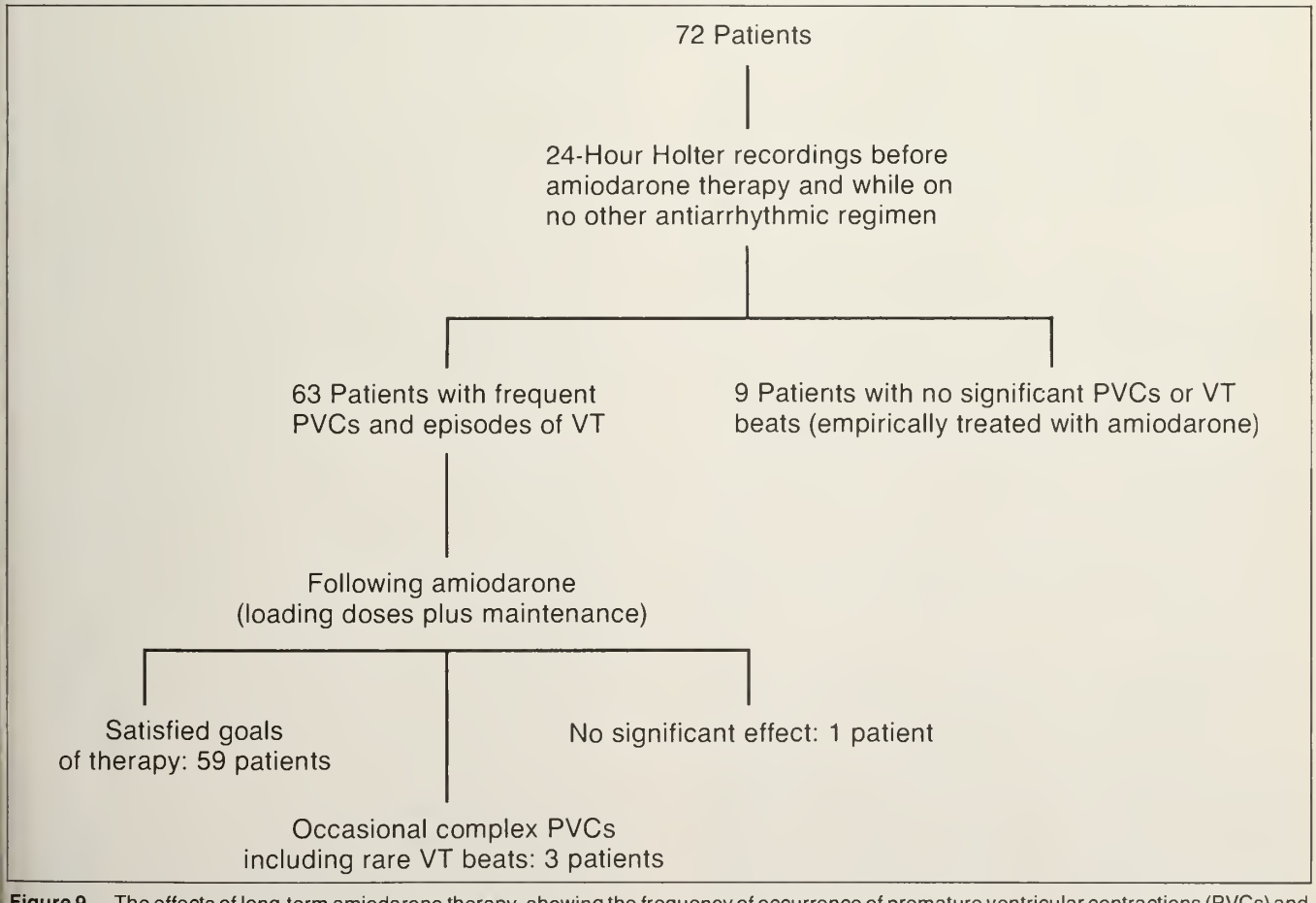
72 Patients
24-Hour Holter recordings before amiodarone therapy and while on no other antiarrhythmic regimen
63 Patients with frequent PVCs and episodes of VT
9 Patients with no significant PVCs or VT beats (empirically treated with amiodarone)
Following amiodarone (loading doses plus maintenance)
Satisfied goals of therapy: 59 patients
No significant effect: 1 patient
Occasional complex PVCs including rare VT beats: 3 patients

Figure 9.—The effects of long-term amiodarone therapy, showing the frequency of occurrence of premature ventricular contractions (PVCs) and ventricular tachycardia (VT) in patients with symptomatic and nonsymptomatic recurrent ventricular tachycardia and cardiac arrest. (From Nademanee et al,[68] with the permission of the authors and *Annals of Internal Medicine.)*

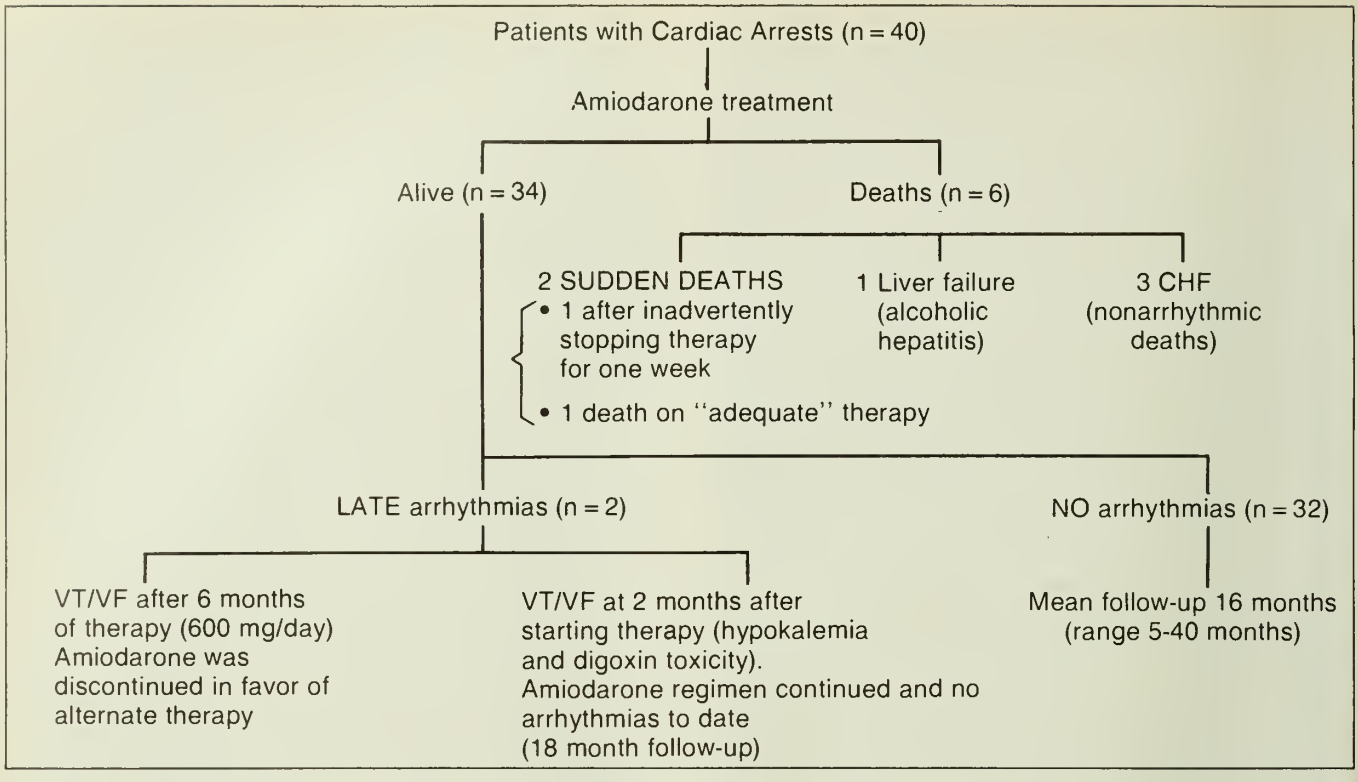
Patients with Cardiac Arrests (n = 40)
Amiodarone treatment
Alive (n = 34)
Deaths (n = 6)
2 SUDDEN DEATHS
• 1 after inadvertently stopping therapy for one week
• 1 death on "adequate" therapy
1 Liver failure (alcoholic hepatitis)
3 CHF (nonarrhythmic deaths)
LATE arrhythmias (n = 2)
NO arrhythmias (n = 32)
VT/VF after 6 months of therapy (600 mg/day) Amiodarone was discontinued in favor of alternate therapy
VT/VF at 2 months after starting therapy (hypokalemia and digoxin toxicity). Amiodarone regimen continued and no arrhythmias to date (18 month follow-up)
Mean follow-up 16 months (range 5-40 months)

Figure 10.—Flow diagram showing the clinical outcome in 40 survivors of sudden cardiac arrests treated prophylactically with amiodarone with initial loading doses and subsequent maintenance doses of the drug. Note the low recurrence rate of arrhythmias during long-term therapy. (From Nademanee et al,[52] with the permission of the authors and the *American Heart Journal.*) CHF = congestive heart failure; VT/VF = ventricular tachycardia/ventricular fibrillation.

were available, the use of amiodarone eliminated ventricular tachycardia beats and reduced the total PVC counts by 90% to 95% during long-term steady-state drug administration. Subsequent serial Holter monitoring showed recordings free of ventricular tachycardia beats with a low rate of PVC occurrence.

Of the 40 patients, 27 underwent electrophysiologic studies. In 21 patients (78%) ventricular tachycardia (in 14 sustained, in 7 unsustained) was reproducibly inducible by programmed electrical stimulation and in 6 patients it was not. Of the 21 patients with inducible ventricular tachycardia, 4 did not consent to the procedure during amiodarone therapy. Of the remainder, ventricular tachycardia reinduction was possible in 11 patients (65%). Despite this high rate of reinduction on a regimen of amiodarone, suppression of complex ventricular ectopy and runs of ventricular tachycardia on 24-hour ambulatory recordings were invariable. Similarly, a salutary clinical outcome was not compromised by the inducibility of ventricular tachycardia during long-term amiodarone therapy.

Our data on the use of amiodarone, with rare exceptions,[82] are consistent with the recent findings of the other investigators[55,83] and permit several conclusions. First, when the drug is used as a single agent in an appropriate dosage regimen, it is extremely effective in controlling life-threatening ventricular tachyarrhythmias, with low incidence of limiting side effects.[68,83,84] Second, in patients in whom an arrhythmia does recur, it is not predictable on the basis of the lack of suppression of inducible VT/VF; the converse also seems to hold, inasmuch as clinical occurrences of ventricular tachycardia were occasionally seen despite the complete suppression by the drug of inducible VT/VF. Third, the drug seems to be extraordinarily potent in suppressing complex ventricular ectopy and total ectopic activity in most patients taking amiodarone over protracted periods. This is in line with the comparable degree of a suppressant effect on ventricular ectopy noted by McKenna[70] in patients with hypertrophic cardiomyopathies who were given amiodarone. Finally, inasmuch as most patients in our series had a near total suppression of ventricular ectopy, and recurrences of clinical VT/VF were not seen, a positive correlation between the two indexes is suggested. Whether there is a causal relation between them, however, remains to be established. It is conceivable, nevertheless, that the suppression of repetitive ventricular ectopy by amiodarone may serve to eliminate the trigger mechanism for the ventricular tachycardia. Furthermore, when ventricular tachycardia does supervene during adequate amiodarone therapy the cycle length of the dysrhythmia is usually long because of a lengthened effective refractory period, and the resulting hemodynamic disturbance is often inconsequential. Both features may be of significance in protecting a patient from the development of ventricular fibrillation, because the latter usually supervenes in the setting of accelerating ventricular tachycardia or deteriorating myocardial function in a patient with underlying cardiac disease.

The overall data with amiodarone emphasize the potential of the drug to enhance survival in patients at risk for recurrent ventricular tachycardia/ventricular fibrillation. Whether other antiarrhythmic agents, such as sotalol and bepridil—which also seem to prolong cardiac repolarization—might be equally effective remains to be determined. In the meantime, a change in the perspective relative to the role of class I versus

class III antiarrhythmics in the control of life-threatening ventricular tachyarrhythmias needs to be critically evaluated.

Our own approach for the drug treatment of life-threatening ventricular arrhythmias takes cognizance of the data discussed above. The exclusion and control of underlying or precipitating causes precedes the development of a therapeutic regimen. In most patients the underlying heart disease is determined (often with cardiac catheterization) and left ventricular ejection fraction measured either by contrast or radionuclide ventriculography. The presence and the nature of the arrhythmia is then documented by multiple Holter recordings or programmed electrical stimulation of the heart, or both, when the patient is not taking antiarrhythmic compounds. The goal of drug therapy is twofold: (1) to suppress spontaneously occurring arrhythmias, especially to eliminate complex ventricular ectopic beats and runs of ventricular tachycardia; and (2) to suppress inducible VT/VF. The available data suggest that the attainment of either goal may represent an adequate therapeutic endpoint for judging long-term antiarrhythmic efficacy. For the present, we initiate therapy on the basis of the Holter and programmed electrical stimulation data from the use of quinidine, procainamide, disopyramide (except in patients with a reduced ventricular ejection fraction) and lidocaine congeners (tocainide and mexiletine).

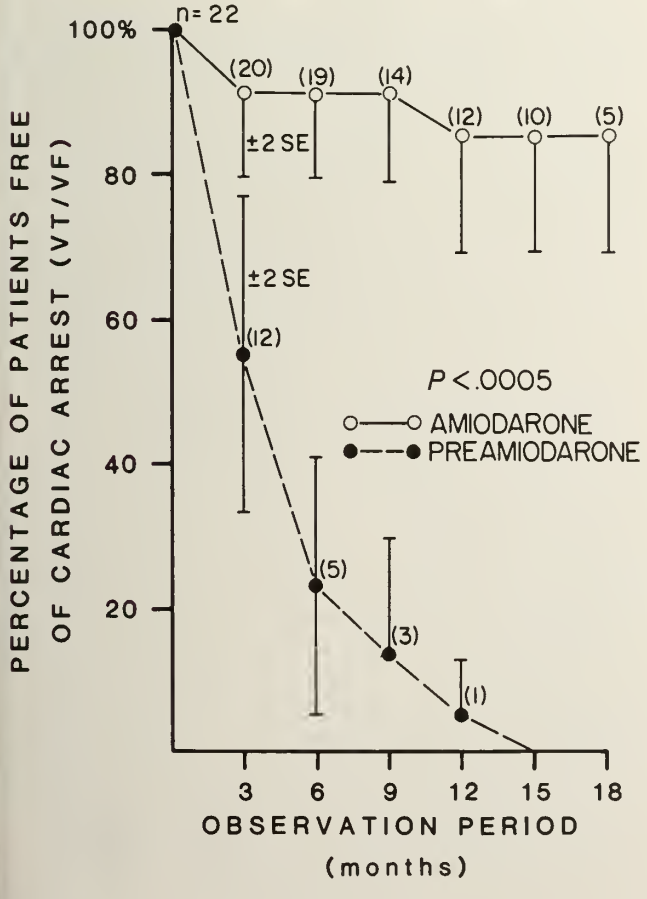

Figure 11.—Effect of the use of amiodarone on the recurrence rate of cardiac arrests in 22 patients with a history of one or more episodes before amiodarone therapy. The analysis was by the life-table method for the period of administration. For each period of follow-up, the recurrence rate on the drug regimen was significantly lower. (Based on data from Nademanee et al.[52]) VT/VF = ventricular tachycardia/ventricular fibrillation, SE = standard error.

Phenytoin, β-blockers and calcium antagonists are rarely used except for specific indications. Before considering surgical treatment or implantable devices in patients who fail when treated with conventional drugs,[89-91] investigational agents,[92] particularly amiodarone,[68] are given an exhaustive trial in view of the apparently extraordinary potency of this unusual compound and of the expanding knowledge of its pharmacokinetics and safety features.[93]

Surgical Treatment of Ventricular Arrhythmias

JOHN H. WITTIG, MD:* Despite considerable advances in our understanding of the mechanisms of clinical ventricular arrhythmias and in surgical techniques, the surgical treatment of ventricular arrhythmias must still be viewed as part of an ongoing investigation in a continuing state of evolution in its various aspects.[94] The main approaches are listed in Table 3.

Sympathetic excitability plays a dominant role in the genesis of ventricular tachycardia in some patients. Thus, from time to time cardiac sympathectomy or denervation has been done in patients with truly refractory ventricular tachycardia.[85] With the advent of β-blockers and other antiarrhythmic compounds, sympathetic ablation is rarely, if ever, done now. However, in some patients with the long QTc-interval syndrome,[37] recurrent VT/VF may occur. In this syndrome, there seems to be an asymmetry between left and right sympa-

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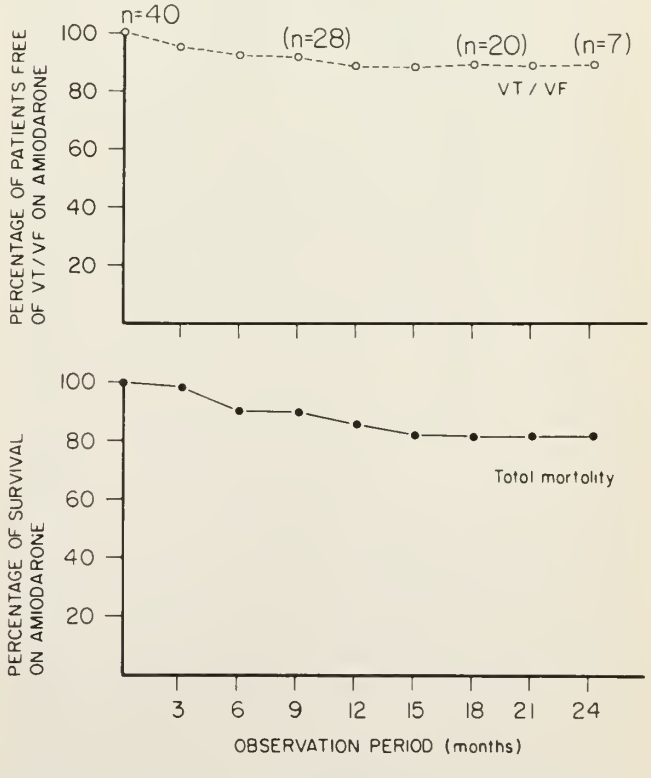

Figure 12.—Effect of amiodarone therapy on total mortality (upper panel) and mortality rate from arrhythmias (lower panel) in 40 survivors of cardiac arrests treated with amiodarone over 24 months. The total mortality was 10%, the mortality from arrhythmia less than 5%. The data indicate that amiodarone has the potential to prolong survival in the survivors of cardiac arrests. (Based on data from Nademanee et al.[52]) VT/VF = ventricular tachycardia/ventricular fibrillation.

TABLE 3.—*Surgical Approaches to the Control of Recalcitrant Life-Threatening Ventricular Tachycardia and Fibrillation*

Local ablation, for example, local excision of tissue in right ventricular dysplasia
Ablation of sources of sympathetic transmitters to the heart
Regional cardiac sympathectomy[85] *
Left stellate ganglionectomy (for recurrent ventricular tachycardia or ventricular fibrillation in the context of long QTc-interval syndromes)[37]
Myocardial revascularization[86]
Non-map-guided aneurysmectomy[72]
Map-guided endocardial ventriculotomy[87]
Map-guided endocardial excision[88]

*The superscript numbers indicate sources from which detailed information may be obtained.

thetic nerve activity; left-sided cervicothoracic sympathectomy, including stellate ganglionectomy, has been reported to normalize the QT interval and to prevent possibly fatal recurrent ventricular tachyarrhythmias.[37]

Coronary artery bypass grafting has also been suggested as a method for controlling ventricular tachycardia in patients with coronary artery disease. However, numerous reports have suggested that myocardial revascularization, alone or in combination with ventricular resection, is usually not effective in the control of recurrent ventricular tachycardia.[95,96] In contrast, recurrent tachycardia that occurs invariably in association with acute ischemic episodes may be eliminated by successful myocardial revascularization.[86] In general, however, myocardial revascularization has not been effective in the control of most cases of VT/VF in patients with coronary artery disease subject to these dysrhythmias.[86,97] In the past, the first direct surgical approach to the control of ventricular arrhythmias was the resection of a ventricular aneurysm (the presumed focus of the arrhythmia) by Couch in 1959.[98] Subsequent experience continues to be sporadic, but, generally, such a blind procedure, even when combined with myocardial revascularization, has yielded less than optimal results in eliminating VT/VF.[72] In one institution, surgical treatment not based on electrophysiologic mapping resulted in a 42% operative mortality (all from recurrent VT/VF and persistent arrhythmias in seven of eleven survivors).[97]

The recent surge of interest in the surgical treatment of recalcitrant ventricular arrhythmias[72] has followed in the wake of the development of accurate electrophysiologic mapping techniques. These have permitted preoperative and intraoperative location of the earliest focus of origin of ventricular tachycardia and the activation sequence[99,100] during the arrhythmia compared with that occurring after sinus activation. Ventricular tachycardia must be present at operation to permit intraoperative mapping and surgical correction, which is feasible because in most patients ventricular tachycardia seems to be due to a relatively protected focal electrical circuit. It lends itself to surgical correction either by endocardial excision[101] or by encircling endocardial ventriculotomy[87]—the two most promising techniques in the surgical treatment of drug-refractory ventricular tachyarrhythmias. Encircling endocardial ventriculotomy has been used largely by Guiraudon and associates[87] in relatively few patients; their results, while promising, are not striking. Our own experience has been essentially with the technique of map-guided endocardial excision in a limited series of patients. The most extensive experience has been reported by Horowitz and associates.[88] They compared the results of standard aneurysmectomy with those of map-guided endocardial excision in their institution. After a standard aneurysmectomy in 71 patients, ventricular tachycardia either persisted or could be reinitiated in 67 patients. These observations indicated the need for extending the surgical resection beyond the limits of standard aneurysmectomy to include the reentrant circuits. Subsequently, when this was done[98] in 79 patients, 7 deaths caused by pump failure occurred within 30 days of the operation. In 70 (of the 72) patients surviving the procedure, electrophysiologic studies were done before discharge. Ventricular tachycardia could not be induced by programmed electrical stimulation in 55. In the remaining patients antiarrhythmic agents, which were previously ineffective, were given long-term. During a limited follow-up, there have been four recurrences of ventricular tachycardia in the 72 patients. These results are clearly encouraging. They indicate that an electrophysiologically guided cardiac surgical procedure has become an important mode of therapy for refractory ventricular tachycardia; its role, however, needs to be further defined and delineated relative to the newer developments in pharmacologic therapy and those in implantable electronic devices.[8]

Role of Implantable Defibrillatory and Antitachycardia Devices

PETER M. GUZY, MD, PHD:* An entirely new departure in the control of cardiac dysrhythmias recently has been the concept of an implantable electronic device with the ability to sense and correct malignant ventricular tachyarrhythmias.[8] Although extremely encouraging, most of the implantable antitachycardia devices are still in the early stages of development and restricted to investigational protocol use. Their use, therefore, remains at present restricted to patients with symptomatic ventricular arrhythmias uncontrolled by antiarrhythmic drugs, those unable to tolerate conventional and investigational drugs, those with hemodynamically compromising tachyarrhythmias noninducible by electrophysiologic testing and those who are not candidates for the surgical control of drug-resistant ventricular tachyarrhythmias.

Various pacing techniques have been developed to date to either terminate or prevent tachyarrhythmias.[102-105] Pacing interruption of reentrant tachyarrhythmias requires critical timing to create a zone of refractory tissue that will block further impulse conduction in the reentrant circuit. Implantable devices designated to deliver single or multiple pacing stimuli have been developed, but their effectiveness is limited by the following factors: distance from the pacing electrode to the reentrant circuit, conduction and refractory properties of the intervening cardiac tissues, size of the reentrant circuit and rate of the intrinsic tachycardia.[105] Tachycardias with longer cycle lengths (slower rates) prove to be more amenable to pacing termination compared with the tachycardias with shorter cycle lengths, which are frequently resistant to pacing interruption. In some instances, antiarrhythmic drug therapy will prolong the cycle length enough to enable pacing termination of the tachyarrhythmia.[106] However, pacing stimuli may inadvertently accelerate an otherwise hemodynamically stable tachycardia and result in clinical deterioration or induce ventricular fibrillation, despite concurrent antiar-

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rhythmic therapy.[106-108] Even when meticulous electrophysiologic testing has shown reproducible pacing termination of at least 100 episodes of the patients' tachyarrhythmia before the implantation of an antitachycardia device, unpredictable tachycardia acceleration, or ventricular fibrillation, has been found sporadically.[102] Therefore, implantable antitachycardia devices without defibrillator capability will probably be inadequate for ventricular tachyarrhythmia control in most patients, though these devices may be sufficiently reliable for control of drug-resistant supraventricular tachycardias.

During the past three years, an experimental-status, implantable automatic defibrillator has been undergoing clinical evaluation in a multicenter, investigational protocol.[109] This device automatically delivers a 25-joule discharge between an intravascular electrode positioned in the superior vena cava and an apical epicardial mesh electrode within 20 seconds after detection of ventricular fibrillation. Recent modifications enable this device to also provide R-wave synchronous cardioversion for ventricular tachycardias faster than the preset heart rate limit. Of 52 patients with a mean follow-up of 14.4 months, 17 experienced 62 successful, out-of-hospital conversions of malignant ventricular arrhythmias by the device. The 22.9% total one-year mortality and the 8.5% sudden-death one-year mortality were lower than the predicted 48% mortality for this patient group without an automatic defibrillator.[8] Another automatic defibrillatory device under development uses a transvenous endocardial electrode system to enable R-wave synchronous cardioversion of ventricular tachycardias at low energy output of 2 joules or less.[110,111] Although R-wave synchronous cardioversions have been done successfully at energy outputs as low as 0.008 joules, acceleration of ventricular tachycardia and hemodynamic compromise or initiation of ventricular fibrillation has occasionally resulted. In addition, supraventricular tachyarrhythmias have also been induced occasionally by the cardioversion or defibrillatory discharges, but these supraventricular tachyarrhythmias have tended to be transient.[110]

In conclusion, implantable devices with antitachycardia and defibrillatory capabilities will be used increasingly in the future as an alternative and an adjunct to both drug and surgical therapy for refractory tachyarrhythmias. Incorporation of a backup pacing capability for bradyarrhythmia control, multiprogrammability for noninvasive adjustment of operational settings and telemetry for determining programmed and measured criteria will make these expensive devices more cost-effective. This will likely give physicians greater flexibility in adjusting a device's operative characteristics to changes in a patient's clinical state, thereby possibly reducing both battery drain and repeated hospital admissions. Although the initial reported experience with an implantable automatic defibrillator suggests a reduction in expected mortality, further studies will be required to determine the impact of these devices on overall patient morbidity and mortality and hence their precise role in the management of life-threatening ventricular tachyarrhythmias.

Conclusion

DR. SINGH: Although data have not been obtained from stringently controlled and blinded protocols, significant inroads may be made into the mortality figure from life-threatening ventricular tachyarrhythmias because of recent advances in antiarrhythmic therapy. New developments have followed closely in the wake of advances in our knowledge of cardiac electrophysiology, particularly the genesis of cardiac arrhythmias. In the clinical laboratory, the relevance of the experimental data may be tested with a particular reference to the nature of clinical arrhythmias and of the fundamental mechanism of action of antiarrhythmic interventions. The newer developments in their wake have raised other questions that provide a fresh impetus for further electrophysiologic and electropharmacologic research.

An antiarrhythmic agent that prevents the induction of VT/VF induced in a controlled state by programmed electrical stimulation may also prevent spontaneous recurrences of the tachyarrhythmia. The data suggest that the converse may not be the case in that the drug amiodarone, an extremely potent suppressant of premature ventricular contractions, so often fails to prevent the induction of VT/VF but provides effective long-term protection against the recurrence of spontaneous arrhythmias in such patients. This does not hold for class I or membrane-active drugs. The fundamental electrophysiologic basis to account for the differences between the response to amiodarone on the one hand and for the class I compounds on the other is not known. Nevertheless, it is a difference that merits study as it may provide further insights into the methods for a more predictable control of malignant ventricular arrhythmias.

Another issue that needs detailed investigation is the relation between a compound's ability to prevent inducible VT/VF and its potency to suppress spontaneously occurring tachyarrhythmias. For example, it is not known whether, in the case of class I agents, it is the same subset of patients in which an effective agent prevents inducible VT/VF and eliminates complex PVCs and runs of ventricular tachycardia in 24-hour Holter recordings. This finding is of immediate therapeutic significance because the available data, discussed in this conference, indicate that both indexes are predictive of long-term efficacy of therapy in life-threatening ventricular tachyarrhythmias. Only a stringently controlled trial in a substantial number of patients followed for a lengthy period is likely to provide a decisive answer. Because an increasing number of newer antiarrhythmic agents with documented potency for near complete suppression of PVCs is becoming available, it is also imperative to establish to what extent PVC suppression may lead to a reduction in the incidence of sudden arrhythmic deaths in patients with heart disease.

The pharmacologic and electrophysiologic advances with the growing therapeutic dividends in their wake must be considered as a continuum with those occurring in the development of surgical techniques and of implantable electronic devices. At present, these modalities are in the early stages of development for the control of ventricular tachyarrhythmias. However, preliminary results from investigations done to date provide cause for the belief that major advances in these areas are likely in the future.

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Medical Staff Conference

Hyperkalemia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143

DR SMITH:* *Potassium is the main cation of intracellular fluid. Its concentrations are carefully regulated through mechanisms still somewhat obscure. Only 2% of potassium is in extracellular fluid. An acute shift of only another 2% into this compartment might well be fatal. In effect, therefore, we live in hazard "below" a huge reservoir of potassium, a modest spillage of which would be incompatible with life. As a consequence, hyperkalemia is not infrequently a medical emergency. In this Medical Staff Conference Drs Miriam Alvo and David G. Warnock will review for us some of the basic mechanisms that maintain potassium homeostasis and the available means of treating hyperkalemia when those mechanisms fail.*

DRS ALVO AND WARNOCK:†‡ Remarkable strides have been made in our understanding of potassium homeostasis. The most exciting advances concern the mechanisms by which the normal intracellular-to-extracellular ratio of potassium is maintained and defended. Hyperkalemia is singled out in this review because it is one of the most lethal electrolyte disorders when improperly managed in the acute care hospital setting. Newer insights into potassium homeostasis have provided a clearer perspective on the causes of hyperkalemia and have placed the therapeutic approaches on a much firmer basis.

The purpose of this review is to integrate this new information into the clinical approach to hyperkalemia. The normal distribution of total body potassium stores will be considered first, followed by a description of how the distribution of potassium stores is regulated. The clinical syndromes of hyperkalemia will be described next. The clinical approach to hyperkalemia will be organized around those factors that acutely regulate the distribution of potassium stores and the factors that affect potassium excretion by the kidney in chronic conditions.

Total Body Potassium Stores

Extracellular potassium concentration is strictly regulated and depends on the interaction between potassium intake, internal potassium distribution and excretion of potassium. Total body potassium is approximately 50 to 55 mEq per kg of body weight (3,500 mEq in a 70-kg person). Intracellular potassium concentrations are 30 times greater than extracellular potassium concentrations and potassium constitutes the main intracellular cation. The maintenance of a high intracellular potassium concentration and a low intracellular sodium concentration is accomplished by the sodium pump (Na^+ K^+ ATPase) located in the cellular membrane. Only 2% of total body potassium (70 mEq) is located in the extracellular compartment; therefore, a relatively small shift of intracellular potassium can result in a significant change in extracellular potassium concentration.

Dietary potassium intake is 70 to 100 mEq per day, 90% of which is absorbed in the upper gastrointestinal tract. Normally, 90% of the absorbed dietary potassium is excreted by the kidneys and 10% is secreted by the colon. Gastrointestinal losses can increase greatly if renal secretion of potassium is impaired.

Regulation of Extrarenal Potassium Homeostasis

The body's immediate response to a potassium load is mainly regulated by extrarenal tissues; 80% of a potassium load is rapidly translocated into nonrenal cells (mainly muscle and liver cells). The renal response is much slower; 50% of the potassium load will be excreted in the urine during the following four to six hours. The extrarenal handling of potassium is affected by insulin, catecholamines, mineralocorticoids, acid-base status and extracellular osmolality.

Insulin

Cellular uptake of potassium by the muscle and the liver is facilitated by insulin. The mechanism by which insulin promotes cellular potassium uptake is not well established, although it appears to be independent of glucose uptake. Moore and co-workers [1] recently proposed that insulin stimulates the sodium-hydrogen exchange in muscle cells; this would increase intracellular sodium and pH, which in turn activates the sodium pump, increasing potassium uptake. The importance of insulin in regulating basal extracellular potassium concentration and the response to an acute potassium load is well established in studies by DeFronzo and associates[2] in which insulin secretion was inhibited by the use of somatostatin in normal controls and in patients with diabetes mel-

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litus. A rise in the basal serum potassium level of 0.6 mEq and decreased tolerance to potassium loads was found in normal subjects and in patients with type II diabetes mellitus. In contrast, serum potassium levels did not change in patients with type I diabetes mellitus (Figure 1). These changes are compatible with the results of suppression of insulin secretion in normal persons and in patients with type II diabetes mellitus; the lack of effect in patients with type I diabetes mellitus is consistent with the absence of endogenous insulin in these patients.

Catecholamines

D'Silva showed that an epinephrine injection produced transient hyperkalemia followed by sustained hypokalemia.[3] Recently DeFronzo and colleagues[4] reported that infusing a dose of epinephrine in humans to physiologic levels reduced the basal serum potassium level and increased the tolerance to a potassium load. Figure 2 shows that potassium chloride

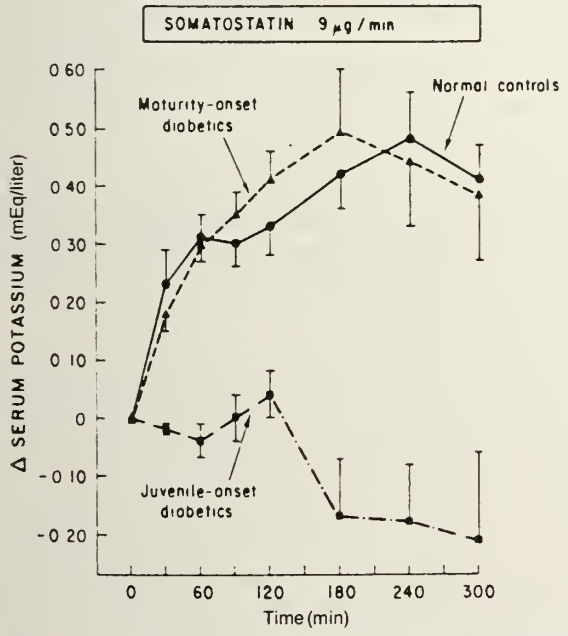

Figure 1.—The effect of somatostatin infusion on serum potassium concentration in normal controls (●), maturity-onset diabetics (▲) and juvenile-onset diabetics (■). (Reprinted with permission from DeFronzo et al.[2])

infusion (open circles) increased plasma potassium by 0.8 mEq per liter at 120 minutes. Pretreatment with epinephrine (open triangles) blunted the rise in plasma potassium during the potassium chloride infusion. The improvement in potassium tolerance was blocked by the simultaneous administration of propranolol hydrochloride (open squares), although propranolol alone had no significant effect on the plasma potassium level. The striking increase in plasma potassium during infusion of epinephrine plus propranolol presumably reflected the α-effects of infused epinephrine.[5] The hypokalemic effect of catecholamines has recently been reported to be mediated through a specific β_2-effect,[6] presumably because β_2-agonists directly stimulate the sodium pump. Propranolol and specific β_2-blockers blunt the hypokalemic response to exogenous epinephrine and also impair the uptake of potassium released from muscle during exercise, so that in patients treated with propranolol hyperkalemia may develop during exercise.[7]

Mineralocorticoids

The role of aldosterone in extrarenal potassium handling is controversial and difficult to assess because it primarily affects renal secretion of potassium. Aldosterone also stimulates potassium secretion by the colon, a factor that plays an important role in potassium regulation in hyperkalemic states associated with impaired renal excretion of potassium.

Acid-Base Status

Changes in acid-base state influence plasma potassium concentration independent of alterations of the external potassium balance.[8] In general acidosis increases potassium release from cells, and alkalosis stimulates potassium uptake by cells. The magnitude of the potassium shift depends on the nature, the severity and the chronicity of the acid-base disturbance. For example, hyperkalemia invariably occurs in metabolic acidosis produced by infusion of mineral acids such as hydrochloric acid or ammonium chloride. In contrast, if organic acids such as lactic acid are infused, only minimal changes in serum potassium are produced. In general, organic acids penetrate the cell more easily and may in fact enter the cell as the nondissociated acid so that no displacement of intracellular cations (potassium) occurs.[9,10] The exact mechanisms involved in potassium shifts during acid-base disturbances are not completely clear, although pH (such as proton concentration) appears to play a role. If serum pH decreases because of an increase in extracellular proton concentration, the gradient favors proton entry into the cell, and potassium might exit in exchange for protons. The reverse may occur during alkalosis. Changes in bicarbonate concentration without changes

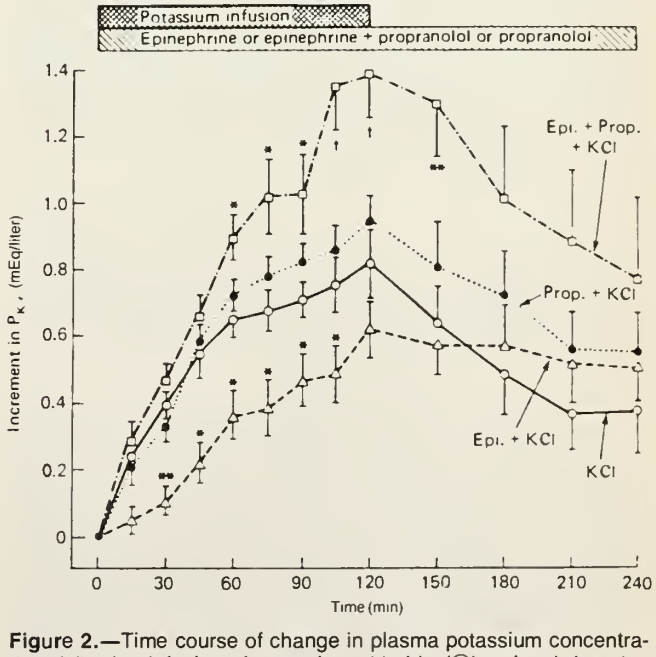

Figure 2.—Time course of change in plasma potassium concentration, following infusion of potassium chloride (○), epinephrine plus potassium chloride (△), epinephrine plus propranolol hydrochloride plus potassium chloride (□) and propranolol plus potassium chloride (●). Asterisk (*) denotes difference from the control values at .05 level of significance, and double asterisk (* *) denotes differences at the .01 level of significance. (Reprinted with permission from DeFronzo et al.[4])

in pH also induce potassium shifts. An increase in extracellular bicarbonate concentration will induce potassium entry into cells and a fall in serum bicarbonate will favor the exit of potassium from cells.[11] In addition, intracellular pH may regulate the activity of the sodium pump; if intracellular acidosis inhibits the sodium pump, potassium uptake into the cells would be inhibited.

Extracellular Osmolality

Extracellular hypertonicity raises the serum potassium level. In anephric animals, hypertonic infusions produce a rise in serum potassium of 0.1 to 0.6 mEq per liter for each 10 mosm per kg of water increase in osmolality. This effect is independent of the nature of the solute producing the hypertonicity. The mechanisms responsible for this effect on extracellular potassium concentration may relate to active potassium chloride extrusion from the cells in response to intracellular hypertonicity.[12]

Regulation of Renal Potassium Excretion

The filtered load of potassium is about 700 mEq per day, 70% to 80% of which is reabsorbed by the proximal tubule and 10% of which is reabsorbed by the loop of Henle. The fraction of potassium reabsorbed in the proximal tubule and loop of Henle remains almost constant, despite 200-fold fluctuations (from 5 to 1,000 mEq) in urinary potassium excretion in response to changes in dietary potassium intake. The factors that regulate renal potassium excretion include diet, pH, distal delivery of flow and sodium and aldosterone.

Diet

The load of potassium in the diet regulates the capacity of the distal nephron to secrete potassium. Animals and humans exposed to a potassium-rich diet can handle a potassium load that would be lethal to animals receiving a normal or a low-potassium diet. This phenomenon is known as potassium adaptation and involves an increase in potassium uptake by non-renal cells and enhanced potassium secretion by the distal tubule and collecting duct. Aldosterone seems to play a permissive role in potassium adaptation.

pH

Acidosis decreases potassium secretion and alkalosis increases potassium secretion by distal and collecting tubule cells. This may reflect changes in intracellular potassium activity, changes in basolateral and luminal permeability to potassium or changes in the activity of the sodium pump.

Distal Delivery of Flow and Sodium

One of the most important variables regulating renal potassium secretion is the rate of fluid and sodium delivery to the distal tubule.[13,14] Two factors might contribute to the accelerated rate of potassium secretion following enhanced distal delivery of fluid and sodium. As sodium reabsorption increases, an increase in transepithelial voltage (increasing luminal electronegativity) would favor potassium secretion. A second factor is the increase in flow rate, which decreases the luminal potassium concentration and maintains a chemical gradient that favors potassium secretion into the luminal fluid.

Aldosterone

Aldosterone stimulates sodium reabsorption and potassium secretion in the cortical collecting tubule.[15] The kaluretic effect of aldosterone depends on an adequate supply of sodium to the distal nephron. The stimulation of potassium secretion involves an increase in luminal permeability to sodium with an increase in luminal electronegativity, an increase in potassium permeability and a stimulation of the sodium pump.

TABLE 1.—*Causes of Hyperkalemia*

Increased Potassium Input
Through diet, salt substitutes
In hemolysis, gastrointestinal bleeding, crush injuries, catabolism
Decreased Renal Potassium Secretion
During inadequate distal delivery of sodium and fluid
Because of impaired renin-aldosterone axis
In Addison's disease, enzyme deficiencies, hypoaldosteronism, hyporeninism, from drugs (heparin, β-blockers, NSAIA, captopril)
From aldosterone antagonists (spironolactones, triamterene, amiloride)
In primary secretory defects
Sickle cell disease, systemic lupus erythematosus, after renal transplant, with obstructive uropathy, interstitial nephritis, congenital or familial primary secretory defects, amyloidosis
Abnormal Potassium Distribution
In acidosis, hypertonicity, from β-blockers, during periodic paralysis, succinylcholine, insulin deficiency, aldosterone deficiency, from exercise, tissue damage, digitalis

NSAIA = nonsteroidal anti-inflammatory agents

Etiology of Hyperkalemia

The major causative factors of hyperkalemia to be considered are increases in potassium input, redistribution of potassium between the intracellular and the extracellular compartments and impaired renal potassium excretion (Table 1).

Increased Potassium Input

Although increased potassium intake can cause hyperkalemia, this is extremely unusual unless an abnormality in internal potassium distribution or impaired renal excretion of potassium is present. Intravenous infusions containing potassium, salt substitutes, transfusions (bank blood 21 days old contains 30 mEq potassium per liter), hemolysis, gastrointestinal tract bleeding, crush injuries and cell catabolism all can raise serum potassium levels. Factitious hyperkalemia can be observed due to thrombocytosis or leukocytosis and is diagnosed by measuring the plasma potassium level.

Abnormal Potassium Distribution

Numerous conditions can affect the distribution of potassium between the intracellular and the extracellular spaces, including acidosis, extracellular hypertonicity, insulin deficiency, aldosterone deficiency, tissue damage, exercise, drugs such as digitalis that in toxic doses impair potassium uptake by the cells blocking the sodium pump, β-blockers that antagonize the action of β_2-agonists and succinylcholine, which depolarizes the cell membrane. Hyperkalemic periodic paralysis is a rare familial disorder characterized by hyperkalemia and a pronounced flaccid paralysis often precipitated by exercise or ingestion of small amounts of potassium (0.5 to 1 mEq per kg).

Decreased Renal Potassium Secretion

Defects in renal potassium handling occur in renal failure if impairment of the renin-aldosterone axis occurs, during therapy with "potassium-sparing" diuretics and in primary disorders of the distal nephron.

Acute renal failure is often accompanied by hyperkalemia, which may become life-threatening, especially in hypercatabolic patients. In cases of uncomplicated acute renal failure (such as in aminoglycoside nephrotoxicity), the serum potassium level should not increase by more than 0.5 mEq per day. In contrast, in chronic renal failure hyperkalemia is rarely a problem. Potassium excretion per nephron and by the colon is increased, and hyperkalemia only develops if dietary potassium is increased or oliguria supervenes. Exceptions are patients with chronic renal failure due to interstitial disease or diabetes mellitus, where hyperkalemia may become a problem if hypoaldosteronism is present.

Impairment of the renin-aldosterone axis occurs in Addison's disease, in selective hypoaldosteronism and in treatment with certain drugs. The lack of aldosterone in Addison's disease will impair renal potassium secretion. In addition, the volume contraction found in this condition will decrease distal sodium and fluid delivery. The destruction of the adrenal medulla decreases epinephrine release, which may contribute to the hyperkalemia by reducing potassium entry to muscle and liver cells.

Selective hypoaldosteronism is found mostly in elderly patients. Nearly all of these patients have low basal renin levels that do not normally increase if a patient is placed in an upright posture. This syndrome is often seen in diabetic patients or in patients with interstitial nephritis.[16] In 75% of the cases the hyperkalemia is asymptomatic and a hyperchloremic metabolic acidosis is present in 50% of the cases. The decreased renin levels have been attributed to a destruction of the juxtaglomerular apparatus by the underlying kidney disease. It is also possible that renin is suppressed by volume expansion due to primary salt retention. In some cases, the primary defect may be in aldosterone synthesis. A blunted secretory response of aldosterone to adrenocorticotropic hormone or angiotensin II infusions has been noted in some cases, and hyperkalemia resulting from the decrease in aldosterone levels would suppress the release of renin and thereby further suppress aldosterone secretion.[17,18]

Many drugs interfere with the function of the renin aldosterone axis at different levels; heparin may impair intrarenal synthesis of aldosterone, β-blockers decrease adrenergic stimuli to renin release, nonsteroidal anti-inflammatory drugs decrease prostaglandin synthesis and thereby inhibit renin release and converting enzyme inhibitors block the generation of angiotensin II from angiotensin I.

Potassium-sparing diuretics affect potassium handling in the collecting tubule. Spironolactone antagonizes the action of aldosterone in the collecting duct by competitive inhibition of aldosterone binding to the cytosolic receptor. Triamterene and amiloride hydrochloride block the luminal entry of sodium into the distal and collecting duct cells, decreasing the luminal electronegativity that normally favors potassium secretion and thereby causing hyperkalemia.

Decreased potassium clearance in the presence of normal aldosterone levels and resistance to exogenous mineralocorticoids has been reported in patients who have primary secretory defects. There are at least two different varieties of this syndrome. Classic pseudohypoaldosteronism is a congenital abnormality in children. The distal tubule is unresponsive to mineralocorticoids, and the syndrome is characterized by salt wasting, hyperkalemia and hyperchloremic acidosis. The syndrome usually corrects spontaneously by the age of 2 to 3 years. The other type of primary potassium secretory defect occurs without salt wasting and is often associated with interstitial kidney diseases.[19,20] This has been described in cases of sickle cell disease and lupus erythematosus and following renal transplantation. An unusual type is the inherited form of pseudohypoaldosteronism, which is characterized by hypertension and hyperkalemia with resistance to correction by exogenous mineralocorticoids.[21]

Clinical Features of Hyperkalemia

The changes induced by hyperkalemia are essentially confined to muscle weakness and abnormal cardiac conduction. A rise in serum potassium reduces the ratio of intracellular potassium concentration to the extracellular potassium concentration, resulting in a decrease in the resting membrane potential (depolarization) towards the excitation (threshold) level. As a consequence, depolarization is delayed, repolarization is accelerated and conduction velocity is slowed.[22,23] Muscular weakness and flaccid paralysis are rare manifestations of hyperkalemia.

The most important effects of hyperkalemia are related to changes in electrophysiologic properties of the heart. The specialized conduction tissue and the atrial and ventricular muscle fibers are affected. The electrocardiogram often reflects these changes. The plasma potassium concentration at which electrocardiographic changes are seen varies, depends on how rapidly the serum potassium level rises and is potentiated by the presence of hypocalcemia. Hyponatremia and acidosis also potentiate the adverse effects of hyperkalemia on the heart.

The earliest electrocardiographic changes are usually narrowing and increased amplitude of the T waves. The QT interval often shortens and as levels of serum potassium increase (generally to over 6.5 mEq per liter), widening of the QRS complex occurs. With serum potassium levels greater that 7 mEq per liter, P waves progressively flatten and broaden and the PR interval increases. At plasma potassium of 8 to 9 mEq per liter, the P waves disappear, and ST changes that suggest ischemic injury or pericarditis may occur. At this point, asystole or ventricular fibrillation is imminent.

Because progression to fatal cardiotoxic reaction is unpredictable, treatment should be instituted without delay if the serum potassium level is above 6.5 mEq per liter even if the results of an electrocardiogram are normal.

Treatment of Acute Hyperkalemia

Immediate treatment should be initiated if an abrupt rise in the serum potassium level to 6.5 mEq per liter or more occurs or if any degree of hyperkalemia associated with electrocardiographic changes is present. Treatment of an acute state includes maneuvers to immediately counteract the effects of potassium at the membrane level, to shift potassium into the cells and to remove potassium from the body.[22,23]

Calcium will increase the threshold potential, reestablishing the difference between the threshold and the resting potential. This approach directly antagonizes the effects of hyperkalemia at the membrane level. A dose of 10 to 30 ml of calcium gluconate (10%) should be administered intrave-

nously over three to five minutes with continuous electrocardiographic monitoring. A second dose may be required. The effect is immediate but only lasts for 30 to 60 minutes. If the patient is receiving digitalis, calcium could be hazardous because the action of digitalis is potentiated

In patients with hyponatremia and hypovolemia, a beneficial effect of sodium chloride has been reported beyond the dilutional effect of volume expansion on hyperkalemia. Sodium may antagonize the effects of potassium on cell membranes. More commonly than sodium chloride, hypertonic sodium bicarbonate is given intravenously (50 to 100 ml of a 7.5% solution). Both the sodium and bicarbonate favor potassium entry to cells.

Atrioventricular block or severe bradycardia that is not reversed in minutes by the above measures is an indication for insertion of a transvenous pacemaker.

Even in the absence of acidosis, bicarbonate will shift potassium into cells. Bicarbonate will also stimulate potassium secretion by the distal tubule by increasing distal sodium delivery and by delivering a relatively impermeant anion to the distal tubule. Sodium bicarbonate infused over a period of five to ten minutes is recommended. The hypokalemic effect starts at five to ten minutes and lasts for two hours. If no effect is seen in 15 minutes, a second bolus can be infused. Secondary effects of sodium bicarbonate infusion include volume overload, seizures due to decreased ionized calcium and increased serum osmolality. Insulin increases potassium uptake by muscle and liver cells. This effect is independent from glucose entry into the cells, but glucose must be administered simultaneously to prevent hypoglycemia; 500 ml of 10% dextrose glucose plus 10 units of insulin infused over one hour is recommended. The onset of the effect is 30 minutes and lasts for four to six hours. The potassium level will decrease by 0.5 to 1.2 mEq per liter in one to two hours.

The above measures will only transiently decrease the serum potassium concentration. More definitive treatment requires elimination of potassium from the body, which can be accomplished by stimulating renal excretion of potassium or by the use of cation exchange resins or dialysis. If renal function is present, administration of saline or sodium bicarbonate is recommended to stimulate potassium secretion by the distal and collecting tubule. Increased distal delivery of sodium can be facilitated by the concomitant use of loop diuretics like furosemide. Sodium polystyrene sulfonate (Kayexelate) will decrease serum potassium by exchanging potassium for sodium in the gastrointestinal tract. Each gram of Kayexelate will remove 0.5 to 1 mEq of potassium in exchange for 2 to 3 mEq sodium. Sodium polystyrene also removes calcium and magnesium and can be administered orally (25 grams per dose) or by a retention enema (50 grams per dose) four to six times a day. Sorbitol should be administered simultaneously to induce diarrhea. The effect begins at one to two hours, and, on average, 50 grams of Kayexelate will lower the serum potassium level by 0.5 to 1 mEq per liter. If these measures are ineffective, or if renal failure is present, hemodialysis and peritoneal dialysis are effective in removing potassium from the body. Potassium clearance with hemodialysis is higher than with peritoneal dialysis. Hemodialysis can remove about 40 mEq of potassium from a hyperkalemic patient in the first hour, whereas peritoneal dialysis will remove between 180 and 240 mEq in 36 to 48 hours.

Treatment of Chronic Hyperkalemia

Chronic hyperkalemia is usually due to decreased secretion of potassium by the kidney. The treatment depends on the specific cause of hyperkalemia. In general, dietary potassium restriction to 40 to 60 mEq per day is recommended. Treatment of acidosis and hypovolemia, if present, will ameliorate the magnitude of the hyperkalemia. Avoidance of drugs that increase serum potassium concentration is recommended, including potassium-sparing diuretics, prostaglandin inhibitors, heparin, β-blockers and angiotensin-converting enzyme inhibitors. If selective hypoaldosteronism is present, mineralocorticoids are the treatment of choice, and large doses are usually required. If Addison's disease is the cause of the hyperkalemia, glucocorticoids and dietary sodium supplementation usually are sufficient but in some patients mineralocorticoid replacement is required. When a distal tubular secretory defect is present, hyperkalemia is in general difficult to treat, but many of these patients respond to thiazides or loop agents. Hyperkalemia due to hyperkalemic periodic paralysis may respond to thiazides. A β_2-agonist (albuterol) has recently been used to treat this condition.[24]

In conclusion, the management of hyperkalemia requires an exact definition of underlying pathophysiology. The acute response to potassium loads and consequently the immediate forms of therapy are directed towards the extrarenal homeostatic mechanisms. Regardless of the cause of hyperkalemia, immediate therapy can be instituted as the diagnostic workup is initiated. Chronic hyperkalemia usually denotes a defect in renal potassium secretion that may respond to maneuvers which increase delivery of sodium to the distal tubule and enhance sodium reabsorption at that site. If renal failure is present, then potassium removal via the gastrointestinal tract or dialysis is required, in addition to careful monitoring of dietary potassium intake.

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Epitomes

Important Advances in Clinical Medicine

Otolaryngology/Head and Neck Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology/head and neck surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in otolaryngology/head and neck surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology/Head and Neck Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Laser Doppler Velocimetry to Predict Skin Flap Survival

WHEN A SKIN FLAP fails to survive (partially or totally), failure is frequently the result of an insufficient blood supply. At the time the flap is created, optimizing the potential for forecasting survival or failure would seem a paramount issue. Oftentimes, evaluating the flap's appearance is enough for a surgeon to feel comfortable with its anticipated outcome. There are, however, occasions when an instrument would be helpful in providing an objective criterion that a surgeon could use to assess effective perfusion of the flap. The laser Doppler velocimeter has been promoted within the past several years as such an instrument.

Laser velocimetry uses a helium-neon laser source transmitting a (632.8-nm) light through optical fibers to a sensor probe. This light is reflected by erythrocytes and in turn received by the probe. Moving erythrocytes cause a frequency shift in the transmitted light. This light reaches a depth of 1.5 mm and measures an area of 1 mm. The readings (in voltage) are of a relative rather than a quantitative nature; in other words, the larger the voltage reading the greater the flow. Many measurements are necessary to evaluate the entire flap.

Two major questions have been addressed in our experience. First, can the laser Doppler velocimeter *predict* flap outcome? Without question, the answer is yes. This has been shown experimentally in random and pedicle flaps and in clinical applications of these flaps. Second, *when* is this predictive capability reliable and useful? Predictions can, with assurance, be made 24 hours postoperatively. For example, this instrument may be used as an aid in determining the proper time for pedicle division. Acute assessment of flow of nutrients at the time of the surgical procedure can be clouded by random erythrocyte movement within the freshly created flap. Both conditions generate a Doppler shift and can be interpreted as blood flow.

In summary, the laser Doppler velocimeter is a useful aid to surgeons when an assessment of flap blood flow is required. It is, however, limited in its effectiveness in the immediate flap development period.

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Emergency Ventilation Using Transtracheal Puncture and Positive Pressure Oxygenation

ACUTE AIRWAY OBSTRUCTION may be managed by endotracheal intubation, emergency tracheotomy or emergency cricothyroidotomy. Even in the hands of experienced practitioners, these modalities are at times difficult to apply. The condition of acute airway obstruction can occur when application of the above techniques is limited either by lack of equipment, lack of experienced personnel or difficulty imposed by the setting itself.

Transtracheal ventilation provides another viable means of rapid access to the airway. The essential equipment includes a 14-gauge plastic-sheathed needle, a 10-ml syringe, a source of high-pressure oxygen (30 to 50 pounds per square inch) with a Luer-Lok connection and a manual interrupter to control respiratory rate.

The plastic-sheathed needle is inserted via the tracheal wall or the cricothyroid membrane. Its location in the trachea is

ascertained by withdrawing air through a small amount of saline in the attached syringe. When the Luer-Lok system is connected, ventilation can be accomplished at standard rates approximating 12 to 15 breaths per minute. An inspiratory-expiratory ratio of 1:3 is adequate. Equipment should include a 10-gauge catheter for secondary puncture of the cricothyroid membrane to allow expiratory flow in the event of total obstruction. Patients are best monitored by observing the excursion of the chest wall and by listening for expiratory air flow at the oral opening.

This technique has been applied with very satisfactory results in patients with progressive airway obstruction due to neoplasia and extensive neck infection. A major problem can occur when total obstruction to expiratory air flow exists, but this is a rare phenomenon. Our initial experience with this technique was obtained in an animal laboratory. It is highly recommended that physicians intending to use transtracheal ventilation develop their experience in that setting. Transtracheal ventilation can be used to considerable advantage in patients with distorted anatomy due to head and neck surgical procedures. The technique may be used to provide ventilation in patients who are otherwise difficult anesthetic cases and who would require either a tracheotomy done while they are awake or a fiberoptic nasal intubation. With the use of transtracheal ventilation, the airway can be stabilized and general anesthesia established, thus saving considerable patient discomfort and operating room time. We have used transtracheal ventilation as the only form of airway control in selected patients undergoing endoscopic examination and biopsy. Results of blood gas monitoring during this form of ventilation have documented very acceptable blood gas measurements over a 30-minute period.

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Retrolabyrinthine Vestibular Nerve Section

SELECTIVE SECTION of the vestibular nerve is effective in relieving intractable vertigo without damaging hearing. This procedure may be indicated for Meniere's disease or for a variety of other conditions that affect the inner ear and produce disabling vertigo, such as temporal bone fractures or labyrinthitis. Until recently an approach through the middle fossa was used to section the vestibular nerve. Recently we have used an approach through the mastoid behind the labyrinth for this purpose. This new approach has resulted in equivalent relief of vertigo and reduced morbidity.

After a patient is given general endotracheal anesthesia, a standard postauricular incision is made and a complete simple mastoidectomy is done. Bone removal is then continued over the posterior fossa dura and the sigmoid sinus into the suboccipital area. The posterior fossa is entered by an incision parallel to the sigmoid sinus posterior to the endolymphatic sac. The fifth through eleventh cranial nerves are easily exposed with minimal cerebellar retraction. The vestibular division of the eighth cranial nerve is separated from the more inferiorly lying cochlear division and sectioned with a fine hook. The mastoid defect is obliterated with strips of fat taken from the abdomen.

We recently evaluated 52 patients who had retrolabyrinthine vestibular nerve section. Of these, 93% reported substantial diminution of vertigo and 86% were able to resume normal activities. None of the patients had complete loss of hearing or facial palsy and there were no serious complications. These results compare favorably with those of middle fossa vestibular neurectomy as an effective means of controlling intractable vertigo while preserving hearing. The morbidity of this procedure is slight and there has been no mortality.

In addition to vestibular nerve section, this approach has also been used for microvascular decompression of the fifth nerve for tic douloureux and of the seventh nerve for hemifacial spasm. Section of the fifth, ninth and tenth cranial nerves for intractable pain due to head and neck tumors is also easily accomplished by this approach.

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Carotid Artery Grafting in Head and Neck Cancer

INVOLVEMENT OF THE carotid artery in malignant head and neck tumors has always carried a very poor prognosis. With the advent of postoperative radiation therapy, myocutaneous flap reconstruction and extracranial to intracranial microvascular reconstruction, however, surgeons can be more aggressive in resecting these lesions.

After completely examining a patient to ascertain the presence of a facial or superficial temporal pulse (indicative of patent common and external carotid systems), a clinician should determine internal carotid artery patency and collateral cerebral circulation by a supraorbital Doppler examination, oculopneumoplethysmography and either intravenous digital subtraction angiography or, most commonly, four-vessel cerebral angiography that shows ipsilateral common carotid compression.

At tumor extirpation, a team consisting of a head and neck surgeon, a vascular surgeon and a neurosurgeon is available. During the radical neck dissection, the collateral cerebral blood pressure is determined via internal carotid artery back pressure readings. A 22-gauge needle is inserted into the common carotid artery to obtain a pressure reading, after which the common and external carotid arteries are clamped and a second reading is taken, this being the internal carotid back pressure. If the back pressure is in excess of 50 mm of mercury, our experience has shown that a patient can tolerate excision of the involved ipsilateral internal carotid artery with small risk of permanent neurologic sequelae.

A back pressure of less than 50 mm of mercury indicates

the necessity for some type of bypass graft. An autogenous saphenous vein graft or Gore-Tex synthetic graft can be used to bridge the common to internal carotid defect if there is an adequate internal carotid stump. In cases of removal of the internal carotid artery at the skull base or in cases of neck infections, autogenous vessels are used to complete an extra-intracranial anastomosis from the common carotid or subclavian artery to the middle cerebral artery. These grafts may then be covered with myocutaneous flaps to protect them from contamination or, in the case of a saphenous vein graft, from occlusion.

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Otolaryngologic Manifestations of Acquired Immunodeficiency Syndrome

THE INCIDENCE of acquired immunodeficiency syndrome (AIDS) is increasing at a near-epidemic rate, with the number of cases doubling every six months. As of January 1984 the number of reported cases was 3,308 worldwide with a three-year death rate of nearly 100%. The syndrome is essentially the dermal malignant lesion, Kaposi's sarcoma, or life-threatening opportunistic infections, or both, in previously healthy homosexual men, Haitians, intravenous drug abusers and blood product recipients without other reasons for immune suppression. The infections are usually fungal, protozoal, viral or mycobacterial in which the T-arm of the immune system is the critical factor. The number of helper cells is reduced, inverting the helper-to-suppressor cell ratio to a mean of 0.4 (normal, 1.8 to 2.4).

Patients often have otolaryngologic and head and neck manifestations. In a retrospective study of 399 patients with AIDS seen at hospitals affiliated with the University of California, San Francisco, 41% had signs and symptoms referable to the head and neck as a chief complaint or as a finding on initial evaluation. Of these signs, 35% were oral, pharyngeal and cutaneous lesions of Kaposi's sarcoma; 8% were rapidly enlarging neck masses due to Burkitt's lymphoma; 31% were oral, pharyngeal, laryngeal and esophageal candidal lesions; 22% were chronic cough and shortness of breath due to infection with *Pneumocystis carinii* or *Mycobacterium avium-intracellulare,* and 4% were labial or oral lesions of herpes simplex. Some patients also had serous otitis, acute mastoiditis, sensorineural hearing loss, parotid mass, sinusitis, emergent airway obstruction, dysphagia or squamous cell carcinoma. Cervical lymphadenopathy was almost a universal finding.

The lymphadenopathy syndrome or "gay lymph node syndrome" warrants consideration because it can present as a neck mass, recurrent pharyngitis or tonsillar hypertrophy and because it is either a prodrome to AIDS or an alternative phenotypic response to the causative agent of AIDS. The lymphadenopathy syndrome is similar to AIDS in both the laboratory findings (mean helper-to-suppressor cell ratio of 0.7) and the constitutional symptoms of fever, night sweats and weight loss. The adenopathy is diffuse, with the posterior cervical chain being the most commonly involved. Lymph node biopsy is being done more frequently because of the appreciation of a purely lymphadenopathic presentation of Kaposi's sarcoma. The biopsy specimens usually show only follicular hyperplasia. Of the 200 patients with lymphadenopathy syndrome followed by Abrams and coworkers, AIDS has developed in eight (D. Abrams, MD, oral communication, August 1984).

The etiologic agent has not been conclusively identified but it is probably viral. As yet there is no single specific diagnostic laboratory test, including the determination of the helper-suppressor ratio. Currently, much of the therapy is specifically directed against the malignant lesion or opportunistic infections. While antibiotics remain a mainstay of treatment, surgical drainage of otitis and sinusitis is helpful in recalcitrant cases, not unlike the management of infection in the preantibiotic era.

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Auditory Brain-Stem Evoked Response Measurement in Infants

THERE IS universal agreement that identifying hearing loss as early as possible enhances the rehabilitative possibilities for an infant with hearing loss. The auditory brain-stem evoked response to click stimuli provides an objective measure of the integrity of the peripheral auditory system and is one well-established procedure by which screening for hearing loss at birth may be accomplished. There are predictable differences in the morphologic characteristics of the infant auditory brain-stem evoked response compared with those in an adult with normal hearing. However, it is possible to identify a clearly replicable waveform at intensity levels near the threshold of hearing. A newborn at risk for hearing loss can be identified by results of auditory brain-stem evoked response showing one of several aberrant findings:

- Absence of an identifiable response at any intensity level.
- Absence of a replicable response at low-intensity levels or
- Increased latencies in one or more of the classic waves (I through V) identifiable in the auditory brain-stem evoked response at high-intensity levels.

Interpretation of results of auditory brain-stem evoked response from a newborn can be complicated by such variables as gestational age of the infant; middle or external ear anomalies, or acoustic stimulus variables, such as click repetition rates, frequency components of the signal and signal duration.

False-positive and false-negative error rates with the auditory brain-stem evoked response procedure among neonates

have not been established, but all reports are unanimous in suggesting that follow-up audiologic evaluations of infants not meeting the screening criteria are mandatory in the first three to four months following discharge. Interpretation to the parents of the consequences of a failure to evoke the auditory brain-stem response in their newborn must be made with caution so they do not assume "deafness" on the basis of such a screening.

Finally, certain types of hearing loss escape identification at birth using this procedure. Therefore, infants whose history or physical findings place them at risk for hearing loss should be examined during the first few months of life regardless of the findings of an auditory brain-stem evoked response at birth.

The integrity of an infant's peripheral auditory system can be evaluated systematically in the first few months of life. Infants at risk for hearing loss should be referred to practitioners experienced in evaluating this disorder. There is no justification for "waiting and watching" the development of an infant until the age of two to three years before referring the child for audiologic evaluation including auditory brain-stem evoked response testing.

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Skin Tests or RAST—Current Concepts

CORRECTLY DONE skin tests (such as serial dilution titration or its equivalent) and the radioallergosorbent test (RAST) both detect IgE antibody with a high degree of accuracy and reproducibility, and both supply information of a quasi-quantitative type. The results of both types of tests generally correlate well with a patient's history and with the signs and symptoms of specific allergens tested. However, the radioallergosorbent test is generally conceded to be somewhat less sensitive than skin tests.

Both RAST and serial dilution titration can be used as the basis for efficient and effective immunotherapy. When RAST values are relied on, a skin test should always be done, using the indicated initial dilution of allergen, before a patient is given a desensitization series.

Skin tests are recognized as superior to RAST in testing for sensitivity to penicillin and Hymenoptera allergens. Skin test results are usually available in about 20 minutes whereas RAST results generally take about two days.

RAST is preferable when generalized dermatologic problems exist or when dermographia is a problem. The economic factor usually favors the use of skin testing over RAST.

In summary, both serial dilution titration skin testing or its equivalent and RAST are reliable methods for assaying IgE-mediated allergens. Skin testing is generally accepted as more sensitive and economical at present. RAST is highly accurate and the method continues to be refined. It is reliable and most helpful when dermatologic problems or other specific situations make skin testing undesirable. When using either method, it is essential that testing be closely monitored by an allergist who is qualified to judge whether the test results correlate well with a careful history and observable signs and symptoms.

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New Approaches to Treatment in Glottic, Subglottic and Tracheal Stenosis

LARYNGOTRACHEAL STENOSIS has long been a difficult management problem for which there is no simple solution. Although it may be congenital, most of the cases we see are acquired. This is due to the increased use of prolonged intubation for mechanical ventilation and the increased incidence of vehicular trauma to the anterior neck.

Endoscopic repair of laryngotracheal stenosis decreases morbidity and mortality. There are patients who simply will not tolerate resection of a tracheal stricture when the risk of morbidity may be up to 20%. In addition, the voice is better after endoscopic procedures than after laryngofissure and the possibility of a later open operation is not jeopardized by initial endoscopic attempts at repair. Dilatation in our experience does not work well unless the scar is so thin that it is almost a mucosa-on-mucosa stenosis.

In a group of 19 patients seen at the University of California, San Francisco, 8 of 9 (89%) cases of posterior glottic stenosis and 9 of 10 (90%) cases of subglottic or tracheal stenosis were successfully treated. These patients were relieved of their shortness of breath and the cannula was removed if they had had a tracheotomy. This was accomplished in most patients with one or two procedures. We were not successful in cases of posterior stenosis if the cricoarytenoid joints were frozen nor in cases of subglottic or tracheal stenosis if the lesion was much longer than 1 cm. The endoscopic technique has been used effectively in a patient with a tracheal lesion that was only 2 cm above the carina.

Glottic stenosis is either anterior or posterior or it can be total. Endoscopic treatment of anterior glottic stenosis is best done with laser and endoscopic Teflon Keel placement. Posterior glottic stenosis is usually due to prolonged intubation and, when the scar completely immobilizes the arytenoids, it can cause apparent bilateral vocal cord paralysis. If a scar band has a mucosa-lined sinus behind it (usually only seen by direct laryngoscopy) it can often be handled by simple laser division. If a scar completely obliterates the posterior commissure and is subglottic or tracheal, then a micro-trapdoor mucosal flap is created to cover the endoscopically removed scar tissue. This is done by excavating the scar starting at the superior aspect of the stenosis in one quadrant. The preserved overlying mucosa is then incised along the lateral aspects, creating an inferiorly based flap. No suturing of the

flap is necessary. This provides a respiratory epithelium to cover the raw area and to decrease scar reformation. The morbidity and mortality in our patients with these techniques have been no greater than those of direct laryngoscopy or bronchoscopy.

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Complications of Injectable Collagen

THE USE OF collagen as an injectable substance for superficial soft tissue augmentation remains relatively new. As "Zyderm Collagen Implant" it underwent the Food and Drug Administration's clinical investigative protocol between September 1979 and August 1981. During this interval, of nearly 10,000 subjects given skin tests, 3% had positive responses. Most reactions were at the test site, although a few persons had arthralgias, flu syndromes or myalgias. Of 5,109 patients subsequently treated, 1.3% experienced adverse reactions despite reports of negative skin test results.

Our experience has shown the same 3% positive skin tests. These reactions have ranged from subtle and transient erythema or induration to pronounced local changes that persisted for many months. Nearly all adverse responses to collagen are manifest within the first two implantations. To avoid complications, each patient should have a skin test twice, with a month-long interval in between. In addition, the patient should be observed closely and questioned regarding any adverse effects.

Annoying but minor reactions follow treatment. Initial erythema and swelling may persist for several hours to days in susceptible persons. Superficial bruising occurs after 10% of treatments and small pustules at needle sites may occur the day after treatment. These can be minimized if the collagen is given by a slow superficial injection after the injection site has been thoroughly cleaned with alcohol and a mild steroid cream applied after injection.

Moderate reactions include visible or palpable lumpiness lasting for from weeks to months and acute or intermittent local edema. The lumpiness is related to the injection technique used and can be avoided with increased experience.

Severe reactions are those related to delayed hypersensitivity. The resulting red-to-purple raised welt is exceedingly difficult to cover, may last for months and is distressing and depressing to patients. The incidence of severe reaction is now well below 1% of those treated, especially if the skin test is done twice. Unfortunately, we cannot predict who will react this way, and no safe and effective treatment exists. The single permanent and disastrous complication thus far reported was a unilateral loss of vision in a patient during a glabellar injection.

One final problem with injectable collagen is the duration of its effectiveness. A significant number of patients will benefit for only 6 to 12 months from a single injection. Therefore, all patients should be informed that they might need yearly injections to maintain a satisfactory result.

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Editorials

Power on the Demand Side of Health Care

SINCE WORLD WAR II this nation has made health and health care top priorities. Experience during the war made it evident that medicine and medical care could really make a difference and after the war medical research was wisely and generously supported by our government. Medical progress was substantial and well publicized. Soon it became a national objective, not only to continue this enormously productive research, but to make its results more readily available for the benefit of all the people. Since the mid-1960s there have been massive programs to make health care available to all by developing and modernizing health care institutions, increasing the numbers of health professionals and providing third party coverage of the costs through health insurance in the private sector and government programs to assure care for needy children, the elderly and the poor. And, most recently, health and fitness has turned out to be something of a national obsession, and a booming business for those who make and sell the supplies and know-how for it. The supply side of health and health care has clearly made great strides, and the rising costs of all this are familiar enough.

While the emphasis has so far been mostly on the supply side, there has also been a growing awareness among the public of the value of health and health care, and their importance to well-being, quality of life and, yes, to prolongation of life. This interest is giving rise to a new demand side for health care whose power to affect what is done about costs has hardly begun to be felt. So far the public does not seem to be as concerned about health care costs as are those on the supply side in both the private and public domain, who are promoting an atmosphere of crisis in health care costs. The public has not yet really spoken on health care costs. However, there is no doubt that the public is impressed with the evidence that medical control of hypertension can reduce strokes, that many forms of cancer (to which they may be susceptible) can now be effectively treated, that such things as coronary bypass operations and hip replacements can enormously improve quality of life, and perhaps even its length. The possibilities of readily available transplants or prosthetic replacements for worn or defective parts excite the imagination to say the least. The public perception is clearly that modern medical care is something worth having. This will surely lead to a greater exercise of power on the demand side of health care, and this will serve to counterbalance the present exercise of power on the supply side, although to an extent that is now difficult to predict.

And where is this power on the demand side to be found? For one thing, as costs are cut on the supply side to the detriment of patient care, these issues are being taken to court, and the courts tend to side with a sick or injured person who has been deprived. It is of note that the American Medical Association has recently decided to challenge, through legal action, the constitutionality of provisions of the Medicare amendments passed with the Budget Deficit Reduction Act of 1984 because they allegedly limit access of patients to care. Special interest groups, such as those who support the right-to-life movement, have already made their power felt on the demand side of health care. And at the other end of the life spectrum, the power of the American Association of Retired Persons (AARP) is beginning to be felt in the political arena of health care. And in the not too distant future, the number of veterans seeking health care is expected to rise sharply—and the power of the veterans' lobby to support its own system of health care is well known. In short, there is real power on the demand side of health care.

One senses that the battle between the supply side and the demand side has yet to be fully joined. Power on each side seems to be of a somewhat similar order of magnitude. How the problem of escalating costs is to be solved in this predictable struggle remains to be seen. It is clear that the opportunities for health and health care and the problems of costs will not go away. One cannot help wondering if cooperation among all those concerned may not be a better answer than the competition and confrontation that now seem to be the order of the day. But in any case, the medical profession will always be found in the patient's corner and on the side of better health and better health care for all our citizens. We will have it no other way.

MSMW

Sudden Cardiac Death—A Perspective

DESPITE A progressive decline in the death rate from cardiovascular disease over the past decade, sudden (arrhythmic) cardiac death remains an imposing challenge, accounting for at least 50% of all cardiac deaths.[1] Recent investigations advancing our understanding of the epidemiology and mechanisms of this problem have been paralleled by improvements and new developments in multiple therapeutic methods, as outlined in the transcript of the UCLA conference elsewhere in this issue.

The title of this conference, "Recent Trends in the Management of Life-Threatening Ventricular Arrhythmias," is broad and merits comment. We now recognize many categories of ventricular arrhythmias. While ventricular fibrillation and sustained ventricular tachycardia are obviously life-threatening arrhythmias, ventricular ectopy, whether complex or simple, is not a life-threatening arrhythmia. Additionally, even most episodes of nonsustained (3 beats to 30 seconds) ventricular tachycardia are asymptomatic and not necessarily life-threatening. Although nonsustained arrhythmias and ventricular ectopy may in some patients be markers of risk for arrhythmic death, the context in which the arrhythmia occurs—that is, the presence, type and severity of underlying heart disease—significantly influences this risk. The most common anatomic substrate associated with sudden death is obstructive coronary artery disease resulting in a previous myocardial infarction, and the vast majority of clin-

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ical and experimental studies examining risk factors, mechanisms and treatment of sudden death have been done in patients with atherosclerotic coronary artery disease. It is premature to assume that similar mechanisms are responsible for sudden death in noncoronary disease. Therefore, in other diseases associated with significant risk for sudden death such as cardiomyopathy, other risk factors may be more appropriate to guide therapy,[2] and different pharmacologic agents may be necessary to prevent this event.

Central to the current approach to recognition, prevention and treatment of sudden cardiac arrest has been the realization that two major perturbations in the course of chronic coronary artery disease may initiate this event: acute, severe ischemia resulting in ventricular fibrillation, and ventricular tachycardia occurring without any apparent provocative factor. The latter appears to be more important statistically, as a few patients dying suddenly show pathologic evidence of acute myocardial necrosis, and most survivors of cardiac arrest do not evolve electrocardiographic or enzymatic evidence of myocardial infarction, nor do they give a history of ischemic symptoms immediately preceding the acute event.

A large body of evidence supports reentry as the most common mechanism underlying ventricular tachycardia in the course of chronic coronary artery disease. For reentry to occur there must be a myocardial substrate with appropriate anatomic and physiologic characteristics, which is activated by appropriate triggers. In the case of ventricular tachycardia, the triggers are usually spontaneous ventricular premature depolarizations and the substrate is an area(s) of abnormal tissue on the border of an old myocardial infarction. If this schema is correct, patients at risk of sustained arrhythmias should be identifiable by the presence of appropriate triggers (using Holter monitoring) or by the presence of a substrate. Identification of a latent substrate has been more difficult, but newer techniques such as programmed stimulation and the signal averaged electrocardiogram[3] may permit this. Similarly, therapy for ventricular tachyarrhythmias could be approached by either eradicating the triggers pharmacologically (the efficacy of which is judged by suppression of spontaneous ectopy on Holter monitors) or disabling the substrate pharmacologically or surgically. The use of programmed stimulation to evaluate antiarrhythmic therapy is based on the ability of conventional antiarrhythmic agents and map-guided surgical treatment to eradicate inducible arrhythmias. Implicit in this model of reentrant arrhythmias is the hypothesis that a therapeutic modality must be effective against only the trigger or the substrate to prevent spontaneous arrhythmias. A corollary of this is that a pharmacologic antiarrhythmic agent that disables the reentrant circuit need not be similarly efficacious in eradicating spontaneous ectopy, and vice versa.[4] A major problem in guiding therapy through suppression of spontaneous ectopy is the remarkable degree of random variation and spontaneous ectopy that many patients show, making interpretation of true therapeutic effects very difficult. In addition, 20% to 25% of patients with documented sustained tachyarrhythmias have only rare and noncomplex spontaneous ectopy. Finally, as only one properly timed ectopic beat is often needed to initiate a tachycardia, it becomes very difficult to completely suppress ectopy without producing intolerable drug side effects. Thus, we have placed greater reliance recently on eradicating the reentrant substrate as the appropriate endpoint for pharmacologic and surgical therapy. Electrophysiologic studies may be helpful not only in identifying drugs capable of preventing inducible arrhythmias, but are equally useful in predicting ineffective drug regimens. By identifying ineffective drugs under safely controlled catheterization laboratory conditions, the risks of empiric trials whose endpoint for failure may be out-of-hospital cardiac arrest are minimized.

Much attention is given in the accompanying symposium to the investigational antiarrhythmic agent, amiodarone. The rosy picture painted of the use of this agent must be tempered by the realization that there are many problems associated with its use. Several large series that have examined the efficacy of this agent in patients having cardiac arrest or sustained ventricular tachycardia have shown that 70% to 80% of patients are free from recurrent arrests or sustained arrhythmias.[5-10] However, in each series side effects (some potentially fatal) necessitating discontinuation of the drug regimen occurred in almost one out of every five patients.[5-10] Thus, only 50% to 60% of patients continue taking the drug and are free of arrhythmias and side effects. Although the drug has no direct negative inotropic effects, it is a noncompetitive adrenergic blocker and has been associated with worsening of congestive heart failure.[6,8,9]

Amiodarone appears to be unique not only in its high degree of efficacy in patients whose arrhythmias have been resistant to conventional agents, but it also appears to work by a different, but as yet unclear, mechanism. In contrast to results with type I antiarrhythmic agents, the ability of amiodarone to suppress ventricular tachycardia induced by programmed stimulation does not appear to correlate with its effects on spontaneous recurrences. The reason for this is not clear at present. Although this drug's effects on intracellular electrophysiologic variables (the primary lengthening of refractoriness) differ from those of type I antiarrhythmic agents, it is not at all clear that this explains its efficacy. In fact, amiodarone does affect the sodium channel and therefore under certain conditions may greatly alter the upstroke of the cardiac action potential, an effect which itself may explain alterations in the tachycardia rate.[11] It is tempting to speculate that the potent suppression of spontaneous ectopy shown by this drug plays a role by interfering with the trigger mechanism for reentrant tachycardias. However, in contrast to the data accumulated by the group at UCLA, not all investigators have shown that suppression of spontaneous ectopy by amiodarone predicts clinical efficacy.[9] Furthermore, the crude clinical measurements available to us at present do not permit us to assume that alterations in arrhythmias such as prolongation of cycle length are necessarily due to specific intracellular effects of drugs such as lengthening of refractoriness. The long duration of action of amiodarone, while beneficial in permitting once a day dosing, has associated problems: the onset of action is delayed and its effects may be prolonged for weeks after the drug is discontinued—that is, when serious side effects develop.

Thus, although we have seen numerous advances in our understanding of "life-threatening arrhythmias," we have far to go. Our understanding of the mechanisms underlying these arrhythmias is incomplete. Although we know slow conduction is a requirement for reentry, a number of conditions may contribute to slowed conduction. For example, while slow

response cells may predispose to slow conduction and these have been found in areas of previous myocardial infarction, most experimental and clinical evidence suggests that cell-to-cell uncoupling rather than intracellular abnormalities are responsible for the slow conduction predisposing to reentry in patients with myocardial infarction.[12,13] Our understanding of the mechanisms by which antiarrhythmic drugs work is incomplete. Studies of the effects of drugs on cellular action potentials alone are inadequate to explain in vivo drug actions in nonhomogeneous infarcted myocardium in which complex reentrant circuits may involve cells with varying degrees of abnormality. Additionally, the conventional classification of antiarrhythmic drugs, as described in this symposium, fails to take into account use-dependent properties of these agents.[14] We are still in need of specific and sensitive noninvasive predictors of patients at risk for cardiac arrest. We have yet to identify the ideal broad-spectrum antiarrhythmic agent that is inexpensive, requires infrequent dosing and is highly efficacious and free of side effects. Electrical therapies for ventricular arrhythmias such as implanted cardioverter-defibrillators require many technologic improvements. Furthermore, these devices are less than optimal in that they do not prevent the occurrence of arrhythmias. Surgical therapy is still evolving, and on the horizon are potentially less invasive therapies such as catheter ablation of arrhythmogenic foci. However, all of these efforts may fail to achieve our most desirable endpoint—improvement in duration and quality of life—if ways are not found to salvage damaged myocardium and improve ventricular function.

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Physicians' Incomes

ACCORDING TO THE AMA Center for Health Policy Research, physicians' average net incomes reached $106,300 last year. The $100,000 figure has been bruited about for some time in the press and elsewhere. And somehow there is an implication that physicians should feel guilty, as though individually or collectively they had done something wrong. While there is no doubt that many physicians have incomes substantially less than this, others—rightfully or wrongly depending on one's point of view—have incomes that are substantially larger. But perhaps the question is, how do physicians' salaries compare with training and responsibilities?

In spite of all the talk—and all the laws—about informed consent and patient responsibility, a patient's life or quality of life is often placed by the patient in the hands of a physician. This is obvious when a patient has given informed consent and is unconscious and being operated on by a surgeon, but it is also often true when a diagnosis is made, or a risky treatment is undertaken, or sometimes even when an x-ray film or a laboratory test is interpreted by a physician specialist in an emergent situation. Where else in our society is there anything like a comparable situation?

Airplane pilots who operate large commercial jet aircraft come to mind. Much as they do with their physicians or surgeons, people place their lives and future well-being in the hands of commercial airplane pilots, and expect them to have the competence and training to do the job, and to exercise expert judgment in the event that something should go wrong.

It is rumored that the salaries of commercial airplane pilots are now approaching if not surpassing $100,000 a year. Is this too in some way wrong? Is it too much? Or are we in fact uncovering something like a going rate of pay for those professionals who have the skill, training, experience and stamina to assume this kind of direct personal responsibility for the lives and future well-being of other people in what can sometimes turn out to be very complex and critical situations? The compensation of physicians, in terms of skill, training, experience and stamina for direct personal responsibility for the lives and well-being of others who are under their care, could become an issue of increasing concern as we find ourselves propelled faster and further into what Eli Ginzberg has called the monetarization of patient care.[1]

MSMW

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Case Reports

Adult Hemolytic-Uremic Syndrome and Bone Marrow Necrosis

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THE TERM "hemolytic-uremic syndrome" was introduced in 1955 by Gasser and associates[1] in a report of five children with acute renal failure, thrombocytopenia and hemolytic anemia. In 1966 a similar disease process in adults was described by Waddell and Matz.[2] Pathologically, hemolytic-uremic syndrome is characterized by the presence of fibrin thrombi, intimal hyperplasia and subintimal fibrin deposition in arterioles.[3] These findings are most prominent in the kidney, but also have been observed in other organs.[3-5] We report the case of a patient with adult hemolytic-uremic syndrome in whom massive bone marrow necrosis developed, a previously undescribed complication.

Report of a Case

A 36-year-old man with idiopathic Addison's disease was admitted to hospital for evaluation of epigastric pain. Results of laboratory tests showed hemoglobin, 12.9 grams per dl; hematocrit, 36.8% (mean corpuscular volume, 75); leukocyte count, 10,700 per μl, and platelet count, 105,000 per μl. Results of a peripheral blood smear were normal except for microcytosis. The prothrombin time was 12 seconds and the activated partial thromboplastin time, 62 seconds. (A circulating anticoagulant had previously been noted.) Results of blood chemistry studies were unremarkable, including creatinine, 0.9 mg per dl, and blood urea nitrogen, 14 mg per dl. Analysis of the urine was normal, except for the finding of 1+ proteinuria. Findings on a bone marrow biopsy done to evaluate the patient's anemia were unremarkable except for absence of stainable iron, and iron deficiency was diagnosed. Upper endoscopic findings showed antral gastritis and achlorhydria.

Two weeks after admission, the patient's condition deteriorated abruptly. Laboratory evaluation at this time showed the following: hematocrit, 25%; leukocyte count, 18,200 per μl; platelet count, 36,000 per μl; a peripheral blood smear contained fragmented erythrocytes; coagulation studies revealed fibrinogen, 230 mg per dl; fibrin degradation products more than 40 μg per ml, less than 80 μg per ml; prothrombin time, 14 seconds; partial thromboplastin time, 54 seconds; lactic dehydrogenase, 530 units per liter; bilirubin, 1.8 mg per dl. Coomb's test results were negative. Analysis of urine showed 2+ glucose, 1+ protein, 2 to 4 leukocytes, numerous erythrocytes and many granular casts. Progressive renal failure developed with values for creatinine, 2.6 mg per dl and blood urea nitrogen, 30 mg per dl initially, rising to 9.3 mg per dl and 142 mg per dl, respectively, over two and a half weeks. Ultimately anuria and increasingly intractable hypertension developed. Progressive hepatic dysfunction was also present, with levels for alkaline phosphatase, 355 units per liter; aspartate aminotransferase 63, units per liter; lactate dehydrogenase, 1,120 units per liter and bilirubin, 1.6 mg per dl. A liver-spleen scan showed focal abnormalities. A liver

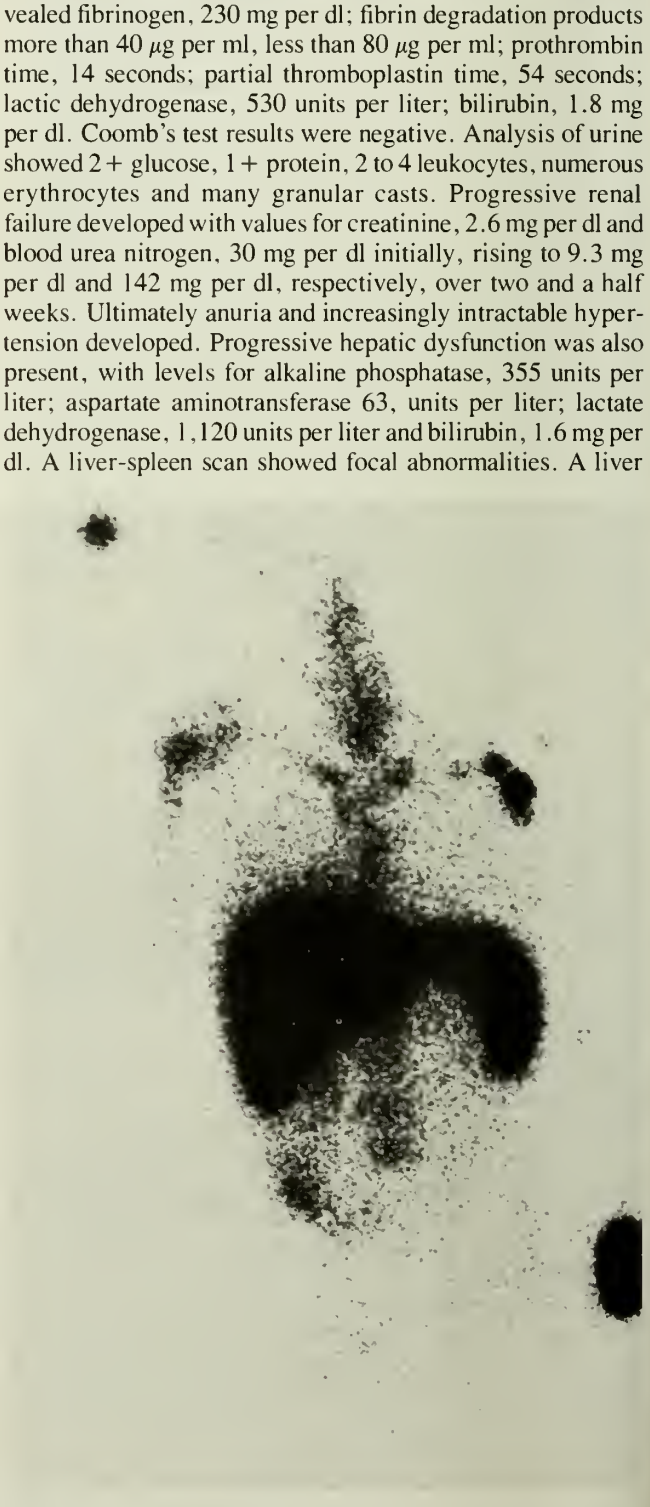

Figure 1.—Technetium Tc 99m minicolloid scan of the bone marrow, anterior view. Normal liver and spleen reticuloendothelial activity is seen. Note the lack of radionuclide uptake in the pelvis and femurs.

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biopsy done with peritoneoscopy showed multiple vascular thrombi, perivascular fibrosis and areas of tissue necrosis.

Complete blood counts obtained serially demonstrated persistent anemia, thrombocytopenia and a leukocyte count that fell to 6,400 per μl within a week. Peripheral blood smear at that time showed nucleated erythrocytes and teardrop forms. Three bone marrow biopsies of the iliac crest, done within two weeks of the initial biopsy, had massive zones of necrosis. Technetium Tc 99m minicolloid scanning and indium In 111 chloride bone marrow scans showed absence of normal pelvic and femoral marrow activity. The vertebrae and right proximal humerus were the only areas of appreciable marrow activity (Figure 1).

Intensive supportive care, including a period of hemodialysis, was provided. A percutaneous renal biopsy done ten weeks after acute deterioration showed arteriolar thrombi and proteinaceous tubular casts (Figure 2).

The patient's blood count remained stable with the hemoglobin in the range of 8 to 9 grams per dl, leukocyte counts about 3,500 per μl and platelet counts in the range of 90,000 per μl. A repeat technetium Tc 99m minicolloid bone marrow scan done four months after the earlier scans showed slight improvement, with new activity noted in the vertex of the skull and in the distal femurs. Pelvic marrow activity remained absent.

Discussion

Our patient had clinical and histologic findings of adult hemolytic-uremic syndrome manifested by prodromal abdominal pain, abrupt onset of thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure, in the absence of laboratory evidence of disseminated intravascular coagulation. Results of renal biopsy were compatible with the diagnosis of hemolytic-uremic syndrome.[6] The demonstration of microvascular thrombi in the liver further supported the diagnosis. Bone marrow necrosis rapidly followed the acute manifestations of hemolytic-uremic syndrome, as shown by biopsy evidence of necrosis seen within two weeks of the previously normal bone marrow biopsy. Marrow scanning confirmed that this necrosis was widespread.

Extrarenal vascular involvement has previously been reported in adult hemolytic-uremic syndrome.[3,5] Most notably, microthrombi have been seen in the bowel, brain, myocardium, pancreas, liver, adrenal glands and lungs. No reports mention bone marrow involvement.

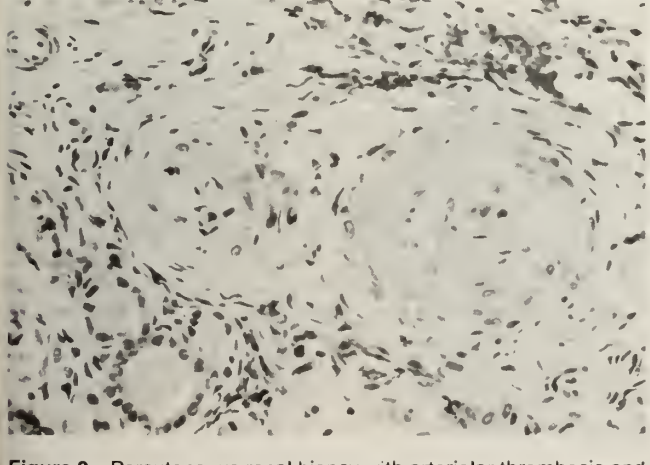

Figure 2—Percutaneous renal biopsy with arteriolar thrombosis and proteinaceous material within a tubule (× 200).

Thrombotic thrombocytopenic purpura shares a number of features with hemolytic-uremic syndrome, including evidence of vascular endothelial damage. In 1952 Cooper and colleagues[7] reported the cases of two patients in whom the clinical diagnosis of thrombotic thrombocytopenic purpura was confirmed by the finding of microvascular thrombi in paraffin sections of small fragments of bone marrow obtained by sternal needle aspiration. In both patients, the marrow itself was hyperplastic. It may nevertheless be speculated that this type of microvascular pathologic feature occurring on a large scale can produce ischemic necrosis of bone marrow.

Bone marrow necrosis is generally believed to be an unusual histologic finding most commonly described at autopsy in patients with leukemia, malignant conditions and sickle cell disease; postirradiation, and in association with certain infections.[8] In living patients, bone marrow necrosis has rarely been reported, although Norgard and associates[9] suggest that this finding may be more common than previously suspected. Harigaya and co-workers[10] described autopsy evidence of widespread bone marrow necrosis in a patient with disseminated intravascular coagulation. In this case no microvascular changes were seen in the kidneys, and it was speculated that marrow necrosis was secondary to multiple intraluminal thrombi in the marrow vasculature.

The presence of a circulating anticoagulant (the lupus anticoagulant) has previously been associated with an increased risk of thrombosis.[11] Four patients in that series also had autoimmune disease, including one patient with adrenal insufficiency, a finding in this patient. A circulating anticoagulant may have predisposed to the marked thrombosis seen in our patient through an unknown mechanism. It is likely that in our patient, the microvascular thrombotic process we felt was responsible for the manifestations of hemolytic-uremic syndrome probably occurred extensively in the bone marrow, resulting in marrow necrosis with pronounced and persistent pancytopenia.

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Tuberculous Involvement of a Polymicrobial Liver Abscess

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HEPATIC INVOLVEMENT by miliary tuberculosis is a common occurrence in 50% to 80% of patients dying of pulmonary tuberculosis.[1] Localized hepatic abscesses, however, are rare—only about 90 cases have been reported in the world literature.[2,3] We report the case of a patient with a single, polymicrobial abscess that also contained *Mycobacterium tuberculosis*.

Report of a Case

A 63-year-old Papago Indian man was admitted to the Arizona Health Sciences Center University Hospital, Tucson, after family members brought him to the San Xavier Indian Health Center. For two to three days he had had greatly increased lethargy, malaise and anorexia, which followed three to four months of weight loss, fatigue and anorexia. He had no recent history of alcohol abuse. He had experienced vague midepigastric pain, particularly after meals, for several months. He also had recurrent urinary tract infections. His illness had not included cough, fever, chills, night sweats, nausca or vomiting.

Four months earlier, the patient had been admitted to hospital for pyelonephritis. During that hospital stay, results of liver function tests were abnormal and an abdominal sonogram showed cholelithiasis but a normal liver.

On physical examination upon admission to the University Hospital the patient appeared lethargic and chronically ill. His pulse rate was 140, respirations 18 per minute, temperature 36°C (96.8° F) and blood pressure 90/60 mm of mercury. There was a documented 14.5 kg weight loss since the admission four months earlier. Examination of the head and neck showed bilateral cataracts. The patient was edentulous. There was no lymphadenopathy. Cardiac examination revealed a regular rhythm with normal S1 and S2 sounds. There was a short grade 1/6 systolic ejection murmur heard over the left sternal border. Lungs had decreased breath sounds and dullness to percussion at the left base; there were no adventitious sounds. Abdominal examination revealed a nontender, nonnodular liver with an 8-cm span. The spleen was not palpable. There were no other masses or tenderness. Results of a rectal examination were within normal limits and the stool specimen was guaiac negative. Extremities had no edema or rashes. Neurological examination showed no abnormalities.

The initial chest roentgenogram showed a left pleural effusion, not present on a radiograph taken four months earlier (Figure 1). No infiltrates were noted. Initial sputum specimens were negative when tested for acid-fast bacilli. Analysis of urine showed the following: a specific gravity of 1.026, 2+ protein, 1+ bilirubin and 75 leukocytes per high-power field. The hemoglobin was 12.5 grams per dl and the hematocrit was 37.4% with normal indices. The leukocyte count was 10,000 per μl with 71% neutrophils, 18% band cells, 3% lymphocytes and 8% monocytes. The platelet count was 216,000 per μl. Results of liver function tests are shown in Table 1.

On the first hospital day, a left-sided thoracentesis was done; the 50-ml specimen of yellow fluid obtained had a leukocyte count of 8,500 per μl with 88% polymorphonuclear leukocytes, 12% monocytes and 500 erythrocytes. Protein was 3.8 and glucose was 121 mg per dl. The lactate dehydro-

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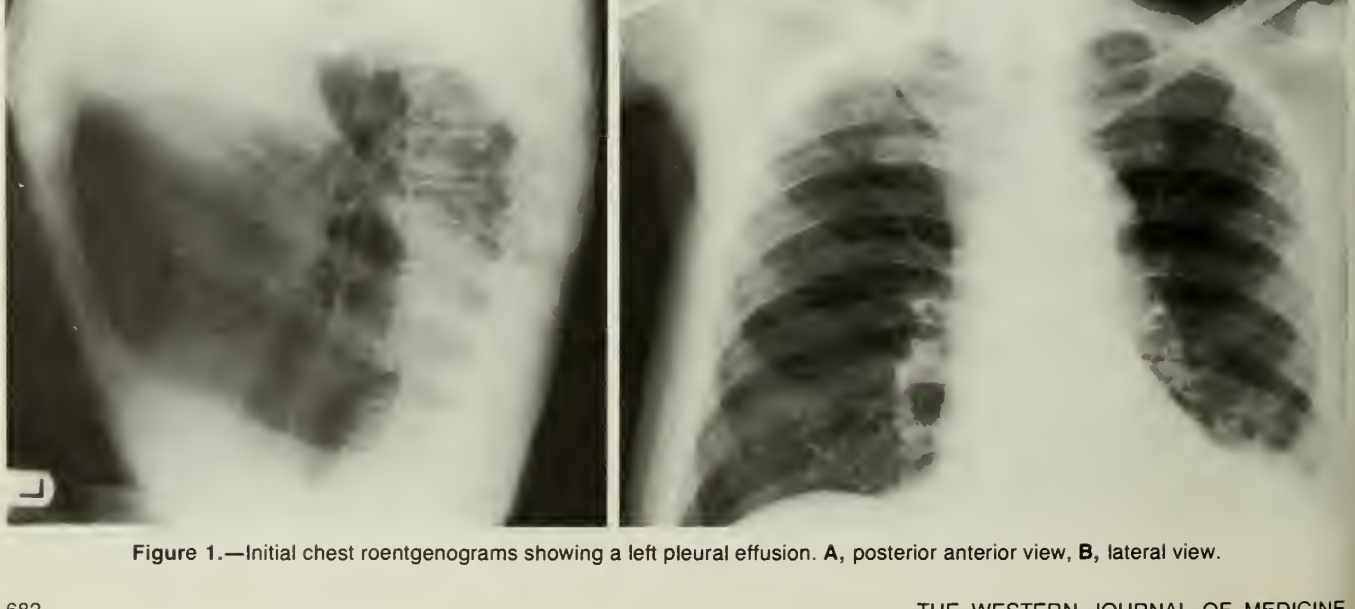

Figure 1.—Initial chest roentgenograms showing a left pleural effusion. **A,** posterior anterior view, **B,** lateral view.

TABLE 1.—*Results of Liver Function Test in a Patient With Tuberculous Disease*

	Total Bilirubin mg/dl	*Alkaline Phosphatase U/liter*	*AST U/ml*	*ALT U/ml*	*Weight (kg)*
07/18/80	1.2	318	43	310	85.4
09/17/80	...	...	...	235	...
10/24/80 (admitted)	2.0	446	38	...	70.9
01/23/80	...	245	61	...	....
05/13/81	...	191	56	...	...
07/02/81	0.9	161	46	37	89.5

AST = aspartate aminotransferase
ALT = alanine aminotransferase

genase value was 4,940 IU per liter. Gram stain and acid-fast bacillus stain of the pleural fluid showed no organisms. The patient was treated with ampicillin and gentamicin. Tests with first strength purified protein derivative, coccidioidin and two control skin tests were negative at 48 hours. The patient's liver function tests persistently showed abnormalities and differential diagnoses of biliary tract disease or possible pancreatic carcinoma were considered. On the fourth day in hospital, real-time sonography identified a 13.5-cm lesion in the left lobe of the liver (Figure 2). Using ultrasound-directed percutaneous aspiration, 50 ml of greenish, cloudy, foul-smelling fluid was removed. The Gram stain of the fluid showed 2+ leukocytes and 3+ pleomorphic Gram-negative rods. Clindamycin and cephapirin were added to therapy with gentamicin; ampicillin administration was discontinued. Smears from the liver abscess aspirate were positive for acid-fast bacilli. Isoniazid, rifampin and ethambutol were added to the above regimen.

The initial bacteriology reports listed four organisms growing from the abscess fluid: *Escherichia coli, Proteus mirabilis, Proteus morgani* and *Bacteroides fragilis.* On the sixth day the patient had a laparotomy for drainage of the abscess cavity; a 200-ml specimen of thick, green, foul-smelling material was removed from the left upper lobe of the liver. The gallbladder and common bile duct were not visualized. Smears from the liver abscess aspirate obtained during the surgical procedure were positive for large numbers of acid-fast bacilli. A sample of sputum taken after the operation was also positive for acid-fast bacilli.

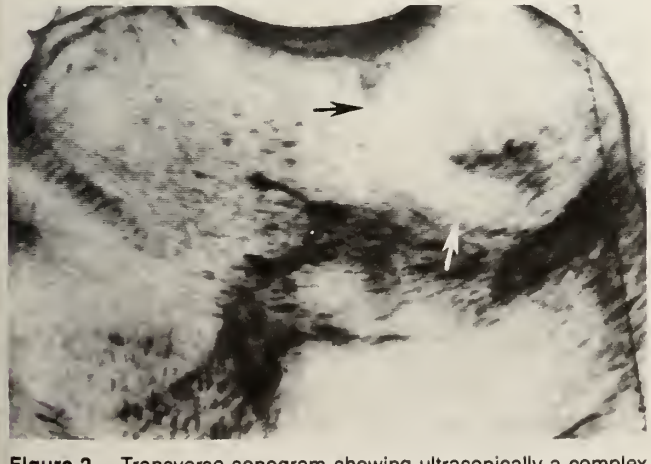

Figure 2.—Transverse sonogram showing ultrasonically a complex mass in the left lobe of the liver. Differential diagnostic considerations included abscess and neoplasm.

Cultures of the sputum, urine, pleural fluid and the liver abscess all eventually grew *Mycobacterium tuberculosis.* After antituberculous therapy was started, the patient slowly returned to his previous level of good health and nutrition. The liver function abnormalities improved and results of a follow-up ultrasound of the liver were normal one year after diagnosis and treatment. Repeated sputum cultures were negative for mycobacteria and a first strength purified protein derivative skin test was positive.

Discussion

Liver involvement occurs in all types of tuberculous disease, including primary pulmonary and miliary tuberculosis. In most cases hepatic involvement is clinically silent. Rarely, solitary or multiple hepatic abscesses are found whether or not the lungs are involved. In patients with chronic pulmonary tuberculosis who have no clinical evidence of extrapulmonary or miliary disease, hepatic abnormalities are found in 50% to 80% of autopsied patients.[4] Bowry and colleagues[5] reported the cases of 37 patients with proven chronic pulmonary tuberculosis who had no evidence of extrapulmonary or miliary disease, but who underwent liver biopsy before antituberculosis therapy. Specimens from 75% of these patients had nonspecific histologic abnormalities, including focal Kupffer cell hyperplasia, fatty metamorphosis and inflammation and dilation of sinusoids. Specimens from 25% of these patients had small noncaseating granulomata, a smaller figure than previously reported in autopsy series.[4,6] Results of tests of hepatic function were only mildly abnormal.

In patients with extrapulmonary tuberculosis, hepatic involvement is common. Korn and co-workers[7] studied 59 patients with extrapulmonary tuberculosis who had liver biopsies; granulomas were observed in 80% and the livers of all patients had histologic abnormalities. Liver function tests showed abnormal values with an elevated alkaline phosphatase level in 41% of the cases. Others have reported elevated alkaline phosphatase levels in patients and extensive granulomatous infiltration of the liver.[8]

Hepatic involvement is also common in miliary tuberculosis—granulomata are found in 80% to 100% of patients at autopsy. Symptoms or signs referable to the liver, however, are seldom the presenting complaints.[9,10]

Tuberculous hepatic abscesses, on the other hand, are rare. Only about 90 cases have been reported in the literature to date. In many ways, our case differs from those previously reported.[3,11,12] A single large liver abscess was found in a patient who had never had evidence of systemic tuberculosis. In retrospect, however, the small pleural effusion represented

tuberculosis of the lungs. Most cases in the literature describe miliary hepatic involvement; liver abscesses with only minimal or no pulmonary or gastrointestinal disease are quite rare.[11]

Tuberculous abscesses in the liver occur most frequently in children and in racial groups felt to have little natural immunity. Our patient, an American Indian, certainly fits into the latter high-risk group. Substandard living conditions and the use of alcohol also play an important role in the high incidence of tuberculosis in this group.

Our patient presented with fatigue, weight loss and vague midepigastric pain. There was no evidence of fever, chills or liver enlargement on physical examination. This is in contrast to the more common presentation, which, according to Leader,[3] includes in order of decreasing frequency: fever, liver enlargement, chills and weight loss. Jaundice is rare. Results of liver function tests have been nonspecific and are similar to those seen with most space-occupying lesions.

Our patient had no pulmonary symptoms and, unlike most patients with miliary tuberculosis,[10] skin tests were negative. The results of liver function studies in our patient were unusual because of the notably elevated alkaline phosphatase value, which initially suggested obstructive biliary disease.

Because the clinical findings are nonspecific, the diagnosis of hepatic tuberculosis is usually made at autopsy or occasionally when a laparotomy is done. Most of the patients described in the literature underwent surgical procedures because of suspected malignant lesion or pyogenic liver abscess. There are also reports of diagnosis from a liver biopsy specimen and occasionally by laparoscopy.[13,14] Both ultrasound and computed tomographic scans have been used extensively for detection and localization of abdominal abscesses.[15-17] The diagnosis of tuberculosis would have been easily missed if proper stains had not been done. Stains of the aspirate were not only positive for many Gram-negative organisms but for acid-fast bacilli as well. An important aspect of this case is that one cause for such an infectious process does not necessarily rule out another cause.

There are several reports of tuberculous liver abscesses being misdiagnosed during surgical procedures.[3] Zipser[11] has noted that bacteriologic confirmation of hepatic tuberculosis has been infrequent—more commonly the diagnosis has been suggested by the microscopic appearance of caseating granulomas.

In summary, our patient was found to have a polymicrobial liver abscess. It is interesting to postulate that he might have developed a Gram-negative bacterial abscess as a result of partial biliary tract obstruction.[18] Subsequently there may have been hematogenous seeding of the liver by tubercle bacilli, possibly from a pulmonary focus. The tuberculosis could have easily been missed, preventing this patient's full recovery, had not the index of suspicion for tuberculosis been high. We suggest that patients found to have defects in the liver, which may suggest carcinoma or liver abscess, be thoroughly investigated for tuberculosis, especially in high-risk populations. Ultrasonically guided fine needle aspiration is a particularly safe procedure for obtaining pathologic material in these patients who are often quite ill.

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Severe Intraoperative Anaphylactic Reaction to Dextran 70 Administered Intraperitoneally

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THE INTRAPERITONEAL administration of high-molecular-weight dextran has recently been proposed to decrease the risk of postoperative adhesion formation. In particular, the use of this agent has been advocated to prevent failure of reconstructive tubal procedures.[1] Whereas the efficacy of such therapy has not yet been convincingly proved in humans, the agent has been claimed to be safe when administered via the intraperitoneal route,[2] We report a case of a severe life-threatening anaphylactic reaction that developed minutes following the intraperitoneal instillation of 32% dextran 70 in a patient receiving the agent in an attempt to prevent adhesion formation.

Report of a Case

The patient, a 66-year-old woman with refractory stage IV ovarian carcinoma, was taken to surgery to have a Tenckhoff

(Markman M, Pfeifle CE, Lucas WE: Severe intraoperative anaphylactic reaction to dextran 70 administered intraperitoneally. West J Med 1984 Nov; 141:684-685)

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Submitted December 20, 1983.

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catheter placed for the intraperitoneal administration of chemotherapy. The patient had no known allergic history and no known prior exposure to dextran. In addition, whereas the patient had a long smoking history, she had no history of cardiac or pulmonary disease, deep venous thrombosis, pulmonary emboli or difficulty with previous surgical procedures. Anesthesia was carried out using halothane and nitrous oxide. Two liters of ascitic fluid were removed at the time of the operation. The catheter was inserted without difficulty. At the completion of the procedure but before extubation, 20 ml of 32% dextran 70 was instilled into the abdominal cavity in an effort to prevent adhesion formation around the catheter. Less than three minutes following the dextran instillation the patient's blood pressure dropped to 30 mm of mercury systolic with the development of an idioventricular rhythm. Diffuse wheezing was noted and an electrocardiogram (ECG) showed diffuse ST-segment depressions. She was given ephedrine, epinephrine, dopamine hydrochloride and steroids. The patient's temperature and pulmonary artery wedge pressure were normal and findings of a chest x-ray film, arterial blood gas determinations, serum electrolytes and cardiac enzymes remained normal. She required pressor agents and massive fluid replacement for about 12 hours, after which time the use of dopamine was gradually discontinued. At this point the patient's neurologic state had returned to normal, the wheezing had disappeared and the ECG findings returned to baseline. Further evaluation elicited no definite cause for the sudden hypotensive event. Specifically, there was no evidence of a myocardial infarction, cardiac tamponade, pulmonary embolus, electrolyte-induced arrhythmia or an infectious episode. It was finally concluded that the patient had experienced an intraoperative anaphylactic reaction to the instilled dextran. She has since received chemotherapy intraperitoneally without major difficulty.

Comment

Dextrans are known potent immunogens. As in our patient, anaphylactic reactions have developed in persons not known to have previous exposure to the agent. However, dextran-producing bacteria are found in the human gastrointestinal tract and in processed sugar products. Despite its immunogenic potential, allergic reactions are uncommon,[3] presumably because of the massive quantities of the agent administered when it is used clinically. In persons surviving severe anaphylactic reactions to dextran, high-titer dextran-reactive antibodies predominantly of the IgG class are found.[3]

Besides our case, there is only a single additional report of an anaphylactic reaction to the intraperitoneal administration of dextran.[4] In that case the reaction developed 75 minutes following the instillation of 300 ml of 6% dextran 75. A recurrence of the reaction developed 20 minutes after the first episode and finally subsided when the dextran was partially removed from the peritoneal cavity.

Our report—and that of Borten and co-workers[4]—emphasizes the danger of intraperitoneal administration of high-molecular-weight dextran. Physicians using these agents to prevent the postoperative development of adhesions must be aware of the small but significant risk associated with the use of these drugs via this route. Whether or not the benefits associated with the intraperitoneal administration of dextran warrant its regular use in practice awaits the completion and analysis of controlled clinical trials.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Pelvic Pain Cured by Pelvic Examination

TO THE EDITOR: I recently read Sargent's interesting report about three cases of pelvic pain apparently cured by pelvic examination,[1] and suggest two nonpsychogenic causes of his three patients' pain.

One possible cause is ovulation: a graafian follicle rupturing from the ovarian surface into the peritoneal cavity (either through the assistance of examination or coincidentally at that moment) would relieve local pressure on the overlying peritoneum. Additional information on the patients' menstrual phases might readily exclude this hypothesis, or offer some support.

Another possibility is rupture of a paratubal cyst, again either spontaneously or through manipulation; such cysts are extremely common incidental findings both in surgical specimens of fallopian tubes removed for other reasons and at autopsy, and usually are clinically silent. Perhaps the patients in the cases reported had oversized cysts of this type, producing pain by stretching of overlying visceral peritoneum; the extraordinarily thin, transparent walls of such cysts break easily with handling, draining their contents and wrinkling their decompressed surfaces. The serous contents of such cysts, like those of follicles, might enter a fallopian tube via fimbriae, and might elicit no peritoneal reaction.

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REFERENCE

1. Sargent E: Unusual pelvic pain apparently cured by pelvic examination (Correspondence). West J Med 1980 Jul; 133:80

Carcinoma as a Possible Complication of Jejunoileal Bypass Operation

TO THE EDITOR: Since the first intestinal bypass for obesity was carried out in 1956, multiple complications have been reported. These include electrolyte and metabolic abnormalities, predisposition to fungal infections, hepatic and renal failure. Although intestinal sequelae of bypass operations are quite common, they have received far less attention. Frequently, patients will present with severe diarrhea postoperatively. This is commonly associated with anorectal pain, itching and burning. These symptoms have been shown to persist for as long as three years in bypass patients.[1] External hemorrhoidal thrombosis, anal fissures, abscesses, rectal inflammation and bleeding have been found on physical examination. There has been, however, no previous report of anal carcinoma in a bypass patient. Such a finding is the basis of this correspondence.

Report of a Case

The patient is a 44-year-old woman with a long history of obesity refractory to conservative management who underwent jejunoileal bypass with end-to-end anastomosis in February 1975. The anastomosis was revised because of inadequate weight loss in May 1976, leaving 46 cm (18 in) of small intestine in continuity. The long blind limb was anastomosed to the sigmoid colon in an end-to-side fashion. Weight loss ensued with three to five liquid movements per day.

In December 1982, the patient presented with symptoms of anorectal pain and bleeding. Repeat outpatient evaluations apparently did not give any specific findings other than "hemorrhoids." In April 1983, because of severe rectal pain, the patient was admitted to hospital and numerous evaluations were done, including digital rectal examination, sigmoidoscopy and barium enema. A definitive diagnosis was not made. The patient referred herself to us because of persistent bleeding and pain in July 1983, and at that time, on rectal examination done following intravenous injection of diazepam, a mass was palpated in the rectum and upper portion of the anus, which on biopsy was moderately well-differentiated squamous-cell carcinoma. In addition, a pelvic mass was appreciated. A computed tomographic scan showed a soft-tissue pelvic mass as well as thickening of the rectum. A bone scan showed no abnormalities.

At exploration, the tumor was found to extend into the bladder. A radical abdominoperineal resection with removal of a portion of the bladder and uterus was carried out. Pathologic evaluation showed squamous-cell carcinoma with 3 of 13 lymph nodes positive for tumor. The patient subsequently received adjuvant radiotherapy.

Jejunoileal bypass patients commonly have anorectal complaints. Some patients, however, are so exquisitely tender that the physician is unable to do a thorough office examination. In these instances, examination under anesthesia and sedation becomes requisite. This case illustrates the error in attributing distressing symptoms such as rectal pain and bleeding to simple hemorrhoids. It is critical that a careful examination of the anus and rectum be performed.

Squamous-cell carcinoma is not usually expected in a 44-year-old patient. Although the occurrence of carcinoma in this patient could well be coincidental, a number of hypotheses might explain a causal relationship between intestinal bypass and the genesis of carcinoma. The purpose of the operation is to induce malabsorption. This change delivers

small bowel contents (for example, bile acids, cholesterol) to large bowel mucosa; such altered gastrointestinal metabolism might predispose to anorectal carcinoma just as dietary changes are thought to predispose to colorectal carcinoma. The role of microflora and bile acids in producing carcinogens or co-carcinogens from substrate in the gut has yet to be elucidated. Finally, the fatty acids and bile acids present in the severe diarrhea could be irritating enough to large bowel mucosa to serve as preliminary antigenic stimulants to a chronic inflammatory response which subsequently becomes dysplastic.

Patients who have had a jejunoileal bypass operation for obesity commonly suffer anorectal complaints. This discovery of anorectal carcinoma in one such patient underscores the importance of an adequate physical examination and workup. Although the occurrence of anal carcinoma in this patient may have been unrelated to the jejunoileal bypass procedure, several sequelae of jejunoileal bypass may predispose to colorectal and anal malignancy.

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Familial Hiatal Hernia

To the Editor: Congenital diaphragmatic defects have been reported to be familial.[1,2] On the other hand, hiatal hernia has generally been regarded as a sporadic nongenetic malformation with practically no risk of recurrence in subsequent pregnancies. A family with six affected persons is presented here. To my knowledge, this is the first report of familial occurrence of hiatal hernias.

A 13-month-old child had a long history of persistent regurgitation dating from the newborn period. She had four to five regurgitant episodes per day. The regurgitation was worse when she was in a horizontal position. She was a product of an uncomplicated pregnancy, full-term normal spontaneous delivery. Birth weight was 3,180 grams. Past health was unremarkable. Paternal great-grandfather, grandmother, grandaunt as well as maternal great-grandmother, grandmother and grandaunt had sliding hiatal hernias confirmed radiologically. Paternal grandaunt, maternal great-grandmother and maternal grandaunt had operative repair of hernias done. The rest of the affected family members were treated with antacids. There is no consanguinity. Physical examinations of the patient showed no abnormalities. Radiographic barium contrast studies of the upper gastrointestinal tract showed pronounced gastroesophageal reflux to the level of the cricopharyngeus.

Hiatal hernia has a multifactorial mode of inheritance although the specific cause is unknown. Most reviews fail to mention the possibility of familial occurrence. The above cases suggest a hereditary factor in the genesis of hiatal hernia. As with other patients with hiatal hernias, the index patient has gross gastroesophageal reflux. Whether this will lead to a sliding hiatal hernia at a later date, for example, through an esophageal stricture formation, is unknown. With such a strong family history, this possibility cannot be excluded.

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Designing New Devices for Measuring Blood Pressure

To the Editor: In their excellent clinical article on effect of stethoscope pressure on blood pressure measurement,[1] Londe and Klitzner did not examine newer devices for blood-pressure monitoring such as digital readout home blood pressure cuffs and Doppler cuffs that do not use a stethoscope but nevertheless do apply a sensor to the skin under pressure. Would these devices also result in artifactual decrease in diastolic blood pressure readings? Judging from the data presented, one would assume that if these instruments were designed so that less than 10 mm of mercury pressure would always be applied by the sensor, they would appear to have a potential advantage in uniformity over fallible human hands—a considerable advantage in blood pressure screening projects of all kinds. One would hope that manufacturers of these new high-tech wonders will take Londe and Klitzner's work into consideration in future design and manufacturing processes.

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Private Sector Financing for Medical Education

To the Editor: Mr Barna astutely noted in his July letter[1] that there seems to be a "physician glut and a coexisting and paradoxical physician shortage." I agree that the production of more physicians will "filter down" fewer doctors for Tulelake than for Beverly Hills. However, few physicians in training base their future practice locale or their specialty choice on the size of their educational debt. Most students are too inundated with scientific esoterica to be concerned with such economic "facts." Our economic naivete is manifest in that there are much better ways for intelligent people to make money than practicing medicine.

Mr Barna also pointed out that the California AHEC program results section did not designate actual numbers of physicians settling in underserved areas. Most physician manpower decisions are based on this type of physician census and physician/population ratios which are inaccurate representations of physician "supply." Ratios exclude such issues as inner city problems of accessibility to professional medical care. A census implies equal productivity for each individual

physician. Maldistribution is a complex issue which is better defined by each community's assessment of its own supply rather than relying on census figures or similar determinations.

As a participant in Ohio's Preferred Placement Program (PPP), I support the concept to finance medical education in return for future services in both rural and urban underserved areas. PPP has developed a financial instrument ($1.5 million) whereby local communities raise private sector monies to finance a student's medical education in return for practice obligations. The physician glut predicted by the Graduate Medical Education National Advisory Committee (GMENAC) encourages the dwindling of government subsidies for medical education. Whether this will filter down to a surplus of physician services for urban and rural underserved communities has yet to be determined. Organized medicine should support and lobby for programs that organize private sector monies for students both to insure equal socioeconomic access to medical education and to help curb maldistribution.

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Oral Contraceptives and Venous Thrombosis

TO THE EDITOR: In his article in the journal[1] on the systemic effects of oral contraceptives, Dr Thomas Kelly states, "In contrast to the controversial relationship between oral contraceptives and arterial occlusive disease, the data regarding the effect of their use on venous thrombosis are quite straightforward." Indeed, they are straightforward; but the scientific interpretation is quite different from that given by Dr Kelly. In a review published in 1973,[2] I pointed out that the association between ingestion of oral contraceptives and venous thrombosis found in retrospective studies could be accounted for by the wide publicity given previously in the medical and lay press of a possible risk of venous thrombosis in oral contraceptive users. As a result, any woman taking the pill and presenting with leg or chest pains would have been carefully examined for evidence of venous thrombosis or pulmonary embolism and many would have been admitted early to a hospital for further studies, such as venography. On the other hand, similar symptoms in a woman not taking the pill might have been dismissed by the patient or her physician as being merely due to leg cramps.

This hypothesis of a greater index of suspicion of venous thrombosis in women using the pill than in nonusers was subsequently supported by the studies of Barnes and coworkers in 1977.[3] They found that the incidence of venous thrombosis proved by Doppler examination in women taking oral contraceptives in whom venous disease was suspected was only 16.7% which was about half the incidence documented by Doppler in women not taking the pill. Furthermore, most prospective studies have not shown an increased incidence of venous thrombosis in women taking the pill. Indeed Dr Ramcharan, the principal investigator in the very large and well-controlled Walnut Creek study, concluded at the end of the study that oral contraceptives as a cause of thromboembolism had not been proved since the effect of diagnostic bias was a strong possibility. Moreover, a cause-and-effect relationship cannot be postulated merely on the basis of a statistical association.

That oral contraceptives induce an increase in certain clotting factors and a slight decrease of antithrombin III is not in dispute. However, no worker with any recent experience in the field of blood coagulation would any more deduce from these facts that these changes tip the hemostatic balance towards thrombosis than they would postulate that a lengthening of the clotting time necessarily indicates hypocoagulability. The facts are now very clear. But although there is no proof that contraceptives predispose towards venous thrombosis, it remains the general belief that a cause-and-effect relationship has been established and this is repeated from one textbook to another without any critical evaluation of the data on which the original claim was based.

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* * *

Dr Kelly Replies

TO THE EDITOR: Dr Hougie suggests that the preconceived impressions of epidemiologists who studied oral contraceptive effects caused them to intensively investigate symptomatic users of oral contraceptives and thus find a spurious association of those agents and venous thrombosis. The designers of early British studies of oral contraceptives were well aware that bias could influence retrospective, case-control studies, and they thoroughly discussed in their reports why bias was unlikely to explain the results they had obtained.[1] In particular, they found that diagnostic studies for venous thromboembolic disease were not employed more frequently in patients using oral contraceptives than in control subjects.[2]

To support his argument that physicians more readily study for thromboembolic disease women receiving oral contraceptives, Dr Hougie references a report in which women referred for Doppler evaluation of leg veins were only half as likely to have confirmation of thrombosis if they were taking oral contraceptives than if they were not. That result, however, is not a universal finding as others have reported observing no difference in the percent of venograms positive for deep venous thrombosis when young women with clinically suspected disease were divided according to oral contraceptive use. Tibbutt found that about twice as many oral contraceptive users were referred for study and at least twice as many had documented thromboses.[3]

Besides retrospective studies, recent prospective studies have also found an association of oral contraceptives and venous thrombosis.[4] Even the Walnut Creek study to which Dr Hougie refers found that oral contraceptive use was associated with an increased risk of idiopathic thromboembolism—that is, thrombosis without a recent surgical procedure, trauma, malignant condition or other known predisposing factor.[5] Some investigators feel that this evidence is weakened by the study's failure to find a statistically significant effect in patients predisposed to venous thromboembolism. They argue that an adverse effect of oral contraceptives should be most pronounced in patients at high risk for thrombosis. However, it can also be argued that other predisposing factors, when present, overwhelm the effect of oral contraceptives and prevent a small but real effect of those agents from being discernible.

In addition to the results of epidemiologic studies, much indirect evidence indicates an association of oral contraceptives and thromboembolic disease. High-dose, noncontraceptive estrogen therapy, such as for suppression of postpartum lactation, has been shown to increase the incidence of thromboembolism.[6] Furthermore, the decreased morbidity from venous thromboembolic disease in reproductive-age women that occurred coincidently with the introduction of contraceptive pills with reduced estrogen content[7] also implicates estrogen as a risk factor for deep venous thrombosis. Finally, the dose-related effect of oral contraceptives to create an apparent imbalance of the hemostatic mechanism towards hypercoagulability, while of uncertain physiologic significance, is consistent with the reported correlation between estrogen dose and the risk of venous thromboembolism.[8]

Thromboembolic events in all young women are infrequent, and so a conclusive answer regarding their incidence in oral contraceptive users as compared with nonusers is unlikely because of the enormous size required of a definitive study. While there is no undeniable proof for a causal relationship between oral contraceptives and venous thrombosis, there is a wealth of evidence for the association of the two which, after reviewing, I and many others have chosen to accept rather than disregard as the result of bias. Yet, I would emphasize that since the risks of oral contraceptive use are small and further reduced by minimizing the steroid content of the preparation used, oral agents are a wise choice for many women who want contraception.

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Relationship Between Costs and Quality of Medical Care

TO THE EDITOR: Your editorial in the August issue dealing with the measurement of quality and costs of medical care[1] reminded me of an interesting proposed relationship between the two. As a student several years ago in the Community Medicine program at the University of Utah School of Medicine I was exposed to the following equation:

$$\text{Quality of Medical Care} = \frac{\text{Outcome of Medical Care}}{\text{Cost of Medical Care}}.$$

Perhaps it was my undergraduate training in mathematics that predisposed me to "latch on" to this equation in such a complete way. Ever since, I have not been able to read an article or editorial dealing with costs and quality without thinking in terms of this relationship.

The beauty of such an expression is that it defines an admittedly "soft" or subjective variable (quality) in terms of two "hard" or more objective variables (outcome, cost). The outcome of a medical care event may be considered in terms of health or functional status, years of life saved or whatever. Costs may include direct costs only or might also include the indirect costs associated with the provision or consumption of that care. To the extent that one increases the value of the numerator while holding the denominator constant or, alternatively, decreases the denominator while holding the numerator constant, quality increases.

I must say, however, that I have always been troubled by my inability to "play" with this equation. For example, if one attempts to move cost from the denominator of the right-hand expression and place it in the lefthand expression what results is as follows: cost · quality = outcome. If one holds quality constant and increases cost, does outcome necessarily increase (improve)? Then if one wishes to move quality into the denominator of the right hand expression (by dividing each side by quality), what results is $\text{cost} = \frac{\text{outcome}}{\text{quality}}$. If one then holds outcome constant and increases quality does cost necessarily go down?

At any rate, given the importance of understanding the relationships between costs of medical care and quality of medical care, we might all benefit from adding this perspective to our conceptual armamentarium.

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Enterococcal Endocarditis After Sigmoidoscopy

TO THE EDITOR: The article by Rodriguez and Levine[1] in the June 1984 issue was timely, indeed. A patient of mine had just been admitted to Santa Monica Hospital with enterococcemia. She was a 67-year-old woman with a porcine mitral valve prosthesis for rheumatic heart disease, a pacemaker and multiple other medical problems.

In reviewing her history and clinical record, we realized she had undergone flexible sigmoidoscopy in December 1983 and did not receive antibiotic prophylaxis. Over the ensuing six months, the patient lost 5 kg (11 lb) of weight, had recurrent bouts of nausea and vomiting and had repetitive episodes of dizziness. Due to the patient's complex set of medical problems and multiple medications, consideration of the diagnosis of prosthetic valve endocarditis was not entertained until June 1984, at which time an astute resident drew blood specimens for culture. Two days later a heavy growth of enterococcus was identified in the blood and the patient underwent a six week course of intravenous antibiotic therapy. No other source for the enterococcemia could be elucidated.

While the 1977 American Heart Association (AHA) guidelines for prevention of bacterial endocarditis clearly recommend antibiotic prophylaxis for patients with prosthetic valves undergoing sigmoidoscopy,[2] a large percentage of endoscopists do not follow these guidelines.[3] Even in retrospect, the gastroenterologist who carried out this patient's sigmoidoscopy felt that prophylaxis was not indicated.

The case described above is at least the third now reported in the literature of enterococcal endocarditis following sigmoidoscopy. Perhaps all endoscopists and primary care physicians would do well to review the AHA guidelines for prophylaxis, particularly as screening flexible sigmoidoscopy is becoming more widespread in primary care offices.

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Methicillin-Resistant *Staphylococcus aureus*

To the Editor: We wish to report three cases of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection in intravenous drug abusers. MRSA is a well-recognized nosocomial pathogen[1,2] and has been identified as a community-acquired pathogen among drug addicts in Detroit.[3] To our knowledge MRSA is not widely recognized as a cause of community-acquired disease in this area.

Reports of Cases

Case 1. The patient, a 45-year-old drug abuser—a "skin popper"—was admitted with multiple cutaneous abscesses, from which grew MRSA (sensitive to chloramphenicol, gentamicin, trimethoprim-sulfamethoxazole and vancomycin). Although blood cultures were negative, a urine culture showed more than 10^5 colonies per ml of MRSA with identical sensitivities.

Case 2. A 32-year-old woman was admitted with MRSA bacteremia (sensitive to chloramphenicol, gentamicin, trimethoprim-sulfamethoxazole, clindamycin and vancomycin). She was a heroin addict who said she had not shared needles. Three months previously she had been admitted to hospital for endocarditis due to a methicillin-sensitive *Staphylococcus aureus*.

Case 3. A 33-year-old woman, a drug abuser, was admitted with chronic osteomyelitis of the symphysis pubis. Blood culture and biopsy of the site revealed MRSA with sensitivities identical to those in case 1. The patient denied drug injection in the groin region.

All three patients had a history of multiple admissions to hospital and frequent antibiotic administration before the admission during which MRSA was recovered.

Traditional empiric therapy for intravenous drug abusers with presumptive staphylococcal infections has included coverage with a penicillinase-resistant antibiotic, typically nafcillin or a first-generation cephalosporin. Our experience suggests that in a seriously ill intravenous drug abuser in whom *Staphylococcus aureus* is suspected, especially when there is a history of recent hospital admission or antibiotic use, empiric therapy should include vancomycin pending culture and sensitivity results.

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Reye's Syndrome and Salicylates

To The Editor: With regard to the role of salicylates in Reye's syndrome,[1] I would suggest an additional comment to Dr Trauner's summary recommendation "to try other means of reducing fever and discomfort in children with viral illnesses and, in particular, flulike illnesses and varicella . . . ." We should also be counseling parents as to the role of fever in the immunological response to infection and to decondition them from using antipyretics routinely when fever and discomfort are modest. My guess is that the association between Reye's syndrome and salicylates would not exist were it not for the large population of children who receive aspirin (and sometimes alternately acetaminophen) on a regular basis for any temperature elevation.

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Commentary

The Disuse Syndrome

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Our cultural sedentariness, recently acquired, lies at the base of much human ill-being. Physical inactivity predictably leads to deterioration of many body functions. A number of these effects coexist so frequently in our society that they merit inclusion in a specific syndrome, the disuse syndrome. The identifying characteristics of the syndrome are cardiovascular vulnerability, obesity, musculoskeletal fragility, depression and premature aging. The syndrome is experimentally reproducible and, significantly, the clinical features are subject to both preventive and restitutive efforts that happily are cheap, safe, accessible and effective.

(Bortz WM II: The disuse syndrome [Commentary]. West J Med 1984 Nov; 141:691-694)

Use is a unifying biologic principle. Vital function is highly keyed to the production of energy. Cybernetic mechanics link optimal performance to regular use. For some body systems (musculoskeletal and cardiovascular) this usage implies physical work. For others usage is defined by the specific function served by the organ, such as sense organs, gastrointestinal tract, genitourinary tract and endocrine system. Even for the systems not primarily serving exercise needs, however, exercise plays a modifying role.

Disuse is catabolic. It adversely affects all body tissues and all body functions. The changes due to it in the particular or in the aggregate contribute substantially to the ill health of our bodies. The mechanisms for the deteriorative effects of disuse are varied and specific to the structure or function involved.

The structural changes accompanying disuse involve such diverse phenomena as loss of muscle fiber bulk, calcium resorption or alteration in the number of membrane-binding sites. The functional changes of disuse similarly are varied, such as disruption of rhythmic processes, loss of enzyme activity or distortion of hormonal responsiveness. Whatever the changes, they are probably tightly linked to the chemical pathways of energy generation. The purpose of this paper is to draw attention to some of the adverse end products of disuse. It is further proposed that many of these results are found so systematically and relatedly in clinical situations to merit their inclusion in a single disorder—the "disuse syndrome." It is hoped that by thus focusing attention on these phenomena, increased preventive and restorative efforts will be directed toward them.

The Long View

In characterizing the results of disuse, it is important to place our current state of inactivity in a historical perspective. Anthropologists delight in regressively resetting the birthdate of sapient humans. The latest reckoning puts the date at least two million years ago. Throughout this extended time our biology was being shaped. Accommodation and compromise decreed who lived and who died. Darwin taught us that our heritage was molded through these eons by physical challenge and threat. The fittest of us survived. In the millions of years we lived as hunter-gatherers, our ancestors were likely extremely physically active, running after or away from their dinner or predators respectively. This life-style persisted until the Agricultural Revolution of 10,000 years ago. Food supply became stationary and physical demands slackened. The Industrial Revolution of 200 years ago greatly accelerated the extent of our inactivity. The time span since this major cultural event is only a twinkling of time—0.0017% of our species' lifetime.

There is a basic anthropologic law called the Principle of Least Effort.[1] Simply stated, when an organism has a task to perform it will seek that method of performance that demands the least effort. The economy implicit in this principle is evident.

The contemporary version of our species seems to have embraced the Principle of Least Effort for its very own. Our ardent pursuit of less effort has led to the wheel, pushbutton tuning, the horizontal escalator and—the embodiment of least effort—the motorized golf cart. A major portion of our industrial complex is committed to the refinement of our inactivity. Great economic advantage seems to accompany any breakthrough that enables us to work less hard. We are perfecting the art of spectating—vicarious exercise. The ultimate eventuality of this trend is frightening to contemplate: *"homo robotis."*

Survival no longer depends on physical prowess. For the hunter-gatherer, the least effort was still hard work. The survival pore through which we squeezed was a tight fit. We

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were hardened and tempered by millions of years of strenuous work. We are the inheritors of fit genes. Two hundred years have greatly redirected the rigor and vigor of human existence.

With the newness of our inactivity, it is not surprising that so little effort has gone into analyzing its effects on us. The space effort, however, changed that. For the first time it became important for us to understand what the effects of prolonged periods of enforced inactivity had on our bodies. Weightlessness accelerates the effects of disuse as countering gravity per se demands work. We went into space with a sparse understanding of the physical threats that it held. We and the Russians are making earnest efforts to fill the gaps in our knowledge of the effects of disuse on our structure and function. Space medicine is the composite of those efforts.

Structural and Functional Responses to Disuse

Musculoskeletal

Perhaps the most graphic example of the atrophic effects of disuse is the limb that has been immobilized in a cast. After only a few weeks of inactivity the muscles shrivel and stiffen. Biopsy specimens of atrophic muscle show a decrease in fiber diameter.[2] The slow-twitch fibers seem especially sensitive to disuse.[3] Increases in urinary nitrogen content are a reflection of the muscle catabolism that accompanies enforced bed rest,[4] bed rest causing a protein loss of 8 grams per day.[5]

Similarly, calcium wastage is uniformly found with inactivity.[6] Both the mineral content and matrix of bone deteriorate. Bed rest results in a calcium loss of 1.54 grams per week.[6] Between 24% and 40% of the mass of the os calcis is lost during 36 weeks of bed rest.[6] The Skylab astronauts lost appreciable amounts of body calcium in space, enough that space flights longer than nine months may not be feasible.

Cardiovascular

The most vital purpose served by our heart and vessels is the transport of oxygen. The maximum oxygen consumption is the best measure of this capacity. A typically unfit American has a maximum oxygen intake that is 40% less than a fit person of the same age.[7] Cardiac output,[8] stroke volume[8] and left ventricular function[9] decrease with disuse, and total peripheral resistance [10] and systolic blood pressure rise.[11]

Orthostatic hypotension and vestibular hypersensitivity have been repeatedly described by the astronauts and cosmonauts. Tilt-table intolerance follows prolonged inactivity.[12] This is at least partially due to a fall in body water that accompanies disuse. Plasma volume falls 10% to 15% with bed rest.[13]

Blood Components

Red cell mass decreases probably as a result of decreased erythropoiesis with inactivity.[8,11] A thrombotic tendency and fibrinolytic activity correlate strongly with prolonged bed rest.[14,15]

Lungs

The work of the lungs is to breathe. When the function is interrupted by bronchial obstruction or pneumothorax, atelectasis and distorted respiratory function ensue.

Gastrointestinal System

Studies of starvation have shown structural and functional changes of all components of the gastrointestinal tract and its appendages.[16] So, too, have many reports described the state of loops of gut when they are excluded from the enteric pathway[17]; mucosal atrophy and glandular shrinkage occur. Total parenteral nutrition provides an interesting study opportunity.[18] The gut needs to be used to retain its functional capacity. The liver atrophies during starvation and constipation and diverticulosis are outcomes of underused gastrointestinal tracts as well.

Genitourinary System

The kidneys when excluded from filtering requirement[19] and the bladder when excluded from storage[20] atrophy and lose vitality.

Reproductive System

Physical inactivity decreases serum androgen levels[21] and spermatogenesis.[22] Cutler and co-workers report that women with regular sexual activity have more regular menstrual cycle lengths[23] than those with less active sexual lives. Masters and Johnson and Kinsey have written extensively on the linkage of good sexual functioning and regular activity.

Endocrine System

Starvation diabetes follows periods of caloric lack. The glycolytic enzymes decrease in amount and activity when carbohydrates are withheld. Physical exercise, however, increases insulin binding sites on muscles.[24]

The necessity for tropic stimulation of the thyroid, adrenal and sex glands is evident. A lack of stimulation promptly leads to deterioration.

Other Regulatory Functions

The body temperature falls[25] and circadian rhythms[24] desynchronize with inactivity. Vernikos-Danellis and associates reported that enforced bed rest resulted in alterations in the normal fluctuations of metabolic and hormonal indices.[26] Glucose response to insulin,[27] adrenocortical response to adrenocorticotropic hormone[28] and growth hormone responses to hypoglycemia[28] are blunted by inactivity. Disuse leads to the breakdown of feedback-integrating mechanisms. Immunologic alterations have also been described with inactivity.[29]

Sensory Deprivation

One of the prime areas for study in the space program has been the phenomenon of sensory deprivation. When subjects are deprived of visual and auditory cues, significant and progressive disorientation occurs. It is interesting to observe that bed rest also has been noted to result in a decrease in visual, auditory[30] and taste acuity.[31]

Nervous System

Physical inactivity results in decreased activity of the sympathomedullary system[32] and there is decreased catecholamine secretion.[33]

Animals raised in a deprived environment, as contrasted to those raised in an enriched environment, solve mazes slower and have smaller brains and sparser dendritic branching.[34] Electroencephalographic alterations and behavioral changes follow prolonged inactivity.[35] The positron-emitting detector clearly shows the correlation between brain use and vital functioning.

This brief survey indicates that all living cells, tissues and organs participate in the syndrome of disuse when their par-

ticular functional activity is impaired. With inactivity so epidemic and universal in our age, it seems appropriate to question whether many of the norms that we apply to functional and structural capacities are in reality faulted and mere descriptors of a lessened potential. This seems to be particularly true of those functions served most highly by exercise demands.

Disease Linkages

Having identified the deteriorative effects that disuse imparts to all body parts, it is logical to inquire how this deterioration may be affecting our overall well-being. My estimate is that the contribution of disuse to human illness is immense. Many sicknesses have components of disuse participating in their pathogenesis, possibly in major degrees.

Mayer has repeatedly drawn attention to the critical role played by inactivity in the development of obesity.[36] There appears to be a highly efficient servomechanism that links energy output with food intake except when inactivity supervenes. Obesity is rare in the wild; it accompanies domestication. Obesity serves survival advantage only when starvation or cold exposure occurs.[37] Otherwise it constitutes a health burden, and its sequelae of degenerative arthritis, hypertension and diabetes compound the problem. Inactivity affects serum lipid values.[38]

Depression responds well to pharmacologic intervention. This prompted the insight into the role of the neurotransmitters in this illness. Peripheral and central nervous system catecholamine content is increased with physical exercise,[33] causing the "runners' high" that is commonly described.[39] It follows that if once we were all more active than we are today, and if physical activity correlates with the mental state, perhaps our entire contemporary sedentary society is depressed.

Disuse certainly participates strongly in changes that are commonly attributed to aging. Indeed, the close correspondence of the alterations ascribed separately to aging and to disuse is striking.[40] Goodrick has reported an 11% to 15% lengthening of the life span of laboratory animals when given an ad libitum opportunity for exercise as contrasted with caged controls.[41]

Stagnation is a derivative of disuse. Whenever a body cavity or duct is rendered stagnant, infection soon follows. The biliary system, the lower genitourinary system, the appendix and so forth reflect this observation.

A number of the above changes are found collectively so frequently and invariably in association with disuse that their aggregation in a clinical syndrome is warranted. The primary characteristics of the disuse syndrome are cardiovascular vulnerability, obesity, musculoskeletal fragility, depression and premature aging. These five features are in many ways interdependent, but all are historical resultants of disuse, as surely as cavitary granulomatous disease is the result of the tubercle bacillus. The features are reproducible in a research setting, and they are correctable by countermeasures. There exist various permutations and formes frustes of the entire syndrome. The syndrome is usually encountered in the middle years of life.

In 1936 Selye first described the concept of the general adaptation syndrome.[42] In his composite thesis he elaborately detailed the body's reaction to excessive input—stress. It is now generally acknowledged that stress and its end products are variably involved in a number of biologic situations. The disuse syndrome can be characterized as the reverse—too little rather than too much. It seems logical that any protracted disruption of the many homeostatic phenomena of our bodies—in one direction or the other—will be harmful.

Discussion

A medical student's first case can be disillusioning. The person's illness does not appear neatly packaged and identified as in the preclinical training. Pathologic conditions do not appear in the way the textbooks say they should. The warp in the clinical presentation of disease is often more impressive than the singular feature of the disease itself. Realization of this fact becomes the challenge and delight of the practice of medicine.

One of the principal distortions of categorical disease is age. Not only do different diseases occur at different ages, but the same disease commonly wears different faces at different ages. A child is not a small adult. An octogenarian is not a wrinkled 20-year-old. Myocardial infarction or a malignant lesion is not the same disease in an 80-year-old person as in a 40-year-old one.

Further, we now know that age corrections are important considerations when assessing some of our basic functional capacities such as arterial oxygen pressure, glucose tolerance, creatinine clearance and others. Identification of the effects of time on disease first led to the establishment of pediatrics as a discipline, and now attention is focusing on the emergence of geriatrics as a major theme of medicine. Disease has an important time dimension.

Illness as we see it has another component that is due neither to disease per se nor to time effects but to disuse, the third dimension.[43] This review is not intended to be encyclopedic with regard to the participation of disuse in our human ailments, but merely to render cohesive what has previously been separately described for each of the circumstances mentioned.

We are blessed with much redundant function. We have two eyes, two ears, two lungs, two kidneys, two testes and two ovaries when only one of them can serve us perfectly adequately. We can run marathons with one lung, or procreate with one ovary or one testicle. The point of this is that we start with 100% of our potential and can surrender 50% with slight or no noted diminution in capacity. It is not until 70% of maximal capacity is lost that a clinical warning sign is lit and medical attention is sought. Unfortunately, a few percentage points of further deterioration mean death. This general observation applies in the lung (oxygen pressure and diffusing capacity), the blood vessels (cross-sectional area), the kidney (creatinine clearance) and the heart (ejection fraction).

Clinical examinations are designed to assess disturbances in the 20% to 30% of maximal range, where disease is manifest. Kerlan has drawn attention to the upper part of the scale, deteriorations from the *norm* that are subclinical.[44(p 22)] This is the range wherein disuse is predominantly manifest. Disuse depletes our reserve capacities and renders us unduly susceptible to disease processes that a fit body may be more easily able to withstand. We are all much more aware of our checking account balance than we are of our health balance.

Inactivity plays a pervasive role in our lack of wellness. Disuse is physically, mentally and spiritually debilitating. But

the good news is that it is almost never too late to recognize this. One of the most extraordinary aspects of the human body is its resilience: its ability to recoup is enormous. The latent period of response from an inactive to an active state can be from seconds (sense organs) to weeks and months but tissues of all ages respond to resumed stimulus with vigor and renewal.

As we progressively identify the adverse effect with which the "least effort" of our culture has seduced us and recognize the extensive benefits that can accrue when the disuse syndrome is combatted, we then can aspire to the biogenetic potential with which our millions of years of vigor have vested us.

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Regionalization of Perinatal Care

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One of a series of articles from western state public health departments

State Public Health Departments can and should assist in reducing infant mortality. The national infant mortality rate is decreasing and the state of Wyoming has played a significant role in this reduction. In 1971 Wyoming had one of the highest infant mortality rates in the nation, ranking 48th among the 51 reporting areas, including the 50 states and the District of Columbia. In 1980 Wyoming ranked second in the nation for low infant mortality. How did this occur?

The northern Rocky Mountain region of the continental United States is a large geographical area with few metropolitan areas and a relatively small population. Many sparsely populated areas are far from sophisticated health centers, creating significant health care delivery problems. In few other fields of medicine does this situation figure more prominently than in the care of high-risk mothers and infants.

The state of Wyoming, with a land mass of almost 100,000 square miles and a population of 470,000 people, is a rural state that has developed a means to provide tertiary care to high-risk infants and mothers through a regionalization program involving medical centers in Colorado, Montana and Utah and secondary centers in Wyoming.

In the foreseeable future, Wyoming's small population base will not be able to support a perinatal tertiary care center. With approximately 10,500 infants delivered yearly in the state's 27 participating hospitals, another solution to the problem was needed.

Enthusiastic and motivated perinatologists from the Denver Children's Hospital and the University of Utah Medical Center in Salt Lake City, with the support of their respective institutions, worked together towards a solution. They emphasized to physicians throughout their catchment area the steps necessary to reduce the newborn mortality rate. These were (1) early recognition of high-risk infants and mothers; (2) vigorous resuscitation and stabilization of neonates; (3) rapid air transport by trained personnel of the neonate to one of the tertiary hospitals. From this beginning, regionalization in Wyoming has grown for the past seven years. There presently is an excellent working relationship between the regional centers and several strategically located level II nurseries within the state. These nurseries are capable of caring for moderately ill neonates for extended periods of time. Severely ill neonates are stabilized and transferred to level III centers.

In 1977 the Wyoming State Health Planning and Development Agency of the Division of Health and Medical Services further addressed the problem of perinatal regionalization by applying for a federal grant available from the US Department of Health and Human Services—the Improved Pregnancy Outcome program. The primary goal of the program was to reduce infant mortality in Wyoming. The funds were granted in 1978 and personnel for the project were hired in December of that year.

There were 34 Improved Pregnancy Outcome programs funded between 1976 and 1980, all in states that had high infant mortality rates. The goal for all the programs was to reduce infant mortality but design and implementation of the programs were left up to each individual program. All were federally funded for five years only, with the understanding that continuation of funding would be at state expense. States receiving Improved Pregnancy Outcome program funds in the area served by *The Western Journal of Medicine* included Nevada, New Mexico, Wyoming, Alaska, Montana, Washington and Arizona.

When the Wyoming Improved Pregnancy Outcome program received federal funding, it was felt that a team approach would be the best way of implementing it. The team included a medical director (pediatrician), program administrator, obstetrical nurse consultant, pediatric nurse consultant, medical social work consultant, nutrition consultant and secretaries.

Through the efforts of the Wyoming Improved Pregnancy Outcome program team—hospital personnel, obstetricians, pediatricians and general practitioners—a peri-

(Meuli RL, Cohen LJ: Regionalization of perinatal care [Public Health and Preventive Medicine]. West J Med 1984 Nov; 141:695-697)

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TABLE 1.—*Wyoming Residents Reported to the Improved Pregnancy Outcome Project and Transported by Air to Tertiary Care Hospitals, 1979-1982**

Year	All Referrals	Obstetric Patients	Infants
1979	73	4	69
1980	156	26	130
1981	206	38	168
1982	275	66	209
Total	710	134	576

* Source: Department of Health and Social Services, Division of Health and Medical Services, Improved Pregnancy Outcome Program, Wyoming.

natal health care group was organized to address the problems of high-risk pregnancies and infants, and to develop a regional referral system. Information about how to care for high-risk perinatal patients was widely disseminated. Consultation from the regional centers was made easily accessible and financial support for air transport to tertiary centers was provided by the Improved Pregnancy Outcome program.

Program planners knew that this regionalization plan would be very costly, but they realized that the cost benefits would justify the program expenditures. The executive and legislative branches of the Wyoming state government appropriated additional funds to insure that all children born in Wyoming would benefit from the regional tertiary care units. Planners felt that for the program to be a success the number of patients transported, especially obstetric patients, should increase as the infant and maternal mortality rate decreased.

Recent results are heartening. More infants thrive now than did five years ago, the transport rate is increasing (Table 1) and the infant mortality rate is decreasing (Table 2).

Wyoming's infant mortality rates were higher than the national average for 16 of the 20 years between 1955 and 1975. In 1971 Wyoming ranked 48th in infant deaths, 39th in 1976, 2nd in 1980 (by residency) and an enviable 1st (by occurrence) in 1980 and 1981.[1-17] In 1980 it was reported that Wyoming had the lowest infant death rate by occurrence in the world.

Wyoming's infant death rates by residency were 27.7 in 1969 and 25.4 in 1972, appreciably higher than 1970 and 1971 (Table 2). The low infant mortality rate for 1970 might be an aberration due to the small numbers.

Intense efforts were made to define the cause and effect relationships responsible for this remarkable improvement in the outcome of high-risk pregnancies. Several factors played a part. During this period there was a pronounced increase in the number of highly trained practicing pediatricians, obstetricians, family physicians and nurses, and hospitals equipped several level I and level II nurseries to better serve high-risk babies. The Improved Pregnancy Outcome program provided education in recognition and care of high-risk neonates. Physicians and nurses were given the opportunity to work in tertiary perinatal units in Denver, Salt Lake City and Billings, Montana, through grants from the Improved Pregnancy Outcome program. Air transport to tertiary units was made available to Wyoming patients, and at least partial funding for individual patient care in tertiary units was provided through legislative appropriations.

Initially, planners felt that the high number of referrals to the program (Table 1) was because health care workers had been made aware that the Improved Pregnancy Outcome project provided funds for transport assistance. Later in the program, the large number of referrals was seen to represent a recognition of the importance of regionalization and a real increase in use of the transport system.

In the early 1970s the regional transport systems came into being. In late 1978 the Improved Pregnancy Outcome program was established. It would appear that in the 1960s and early 1970s, when Wyoming infants were being cared for in Wyoming, many were dying in their local communities. In the mid-1970s Wyoming was having more than its share of infant deaths, but some of the neonates were dying in regional centers out of state. By the early 1980s, infants' problems were being recognized and managed appropriately, so that more were surviving both in and out of state. Provisional data for 1982 for Wyoming indicate an infant mortality rate of 6.3 per 1,000 live births by place of occurrence[18] and a rate of 9.9 per 1,000 live births by place of residency.[19] This would suggest that Wyoming's reduction of infant mortality is being maintained.

Wyoming is one rural state that has benefited greatly from regionalization. The success of coordination and cooperation among states, their health departments and the regional medical centers is apparent in the results of this program. These data present a strong argument for the

TABLE 2.—*Comparison of Wyoming Infant Mortality Rates and Those of the United States for Selected Years, 1970-1981**

Year	Total Births	Infant Deaths	Wyoming Mortality Rates†		US Mortality Rates*	State Rank ‖	
			Residence ‡	Occurrence §		Residence	Occurrence
1970	6,502	130	20.0	18.9	20.0	29th	19th
1971	6,120	150	24.5	21.1	19.1	48th	41st
1975	6,962	121	17.4	14.7	16.1	38th	20th
1976	7,380	122	16.5	14.3	15.2	39th	20th
1980	10,562	103	9.8	6.6	12.5	2nd	1st
1981	10,814	115	10.6	6.7	11.9	15th	1st

* From National Center for Health Statistics.[4-17]
† Deaths of children less than 1 year of age per 1,000 live births.
‡ Rates are calculated by usual residence of mother.
§ Rates are calculated by place of death of the infant.
‖ State rank is calculated from lowest infant mortality rate to highest, and includes the 50 states and the District of Columbia.

use of public funds for education of perinatal health care providers and development of prevention programs.

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Information

Diagnosis and Treatment of Myocardial Disease in Infants and Children

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MYOCARDIAL DISEASE in infants and children is a spectrum of cardiac muscle dysfunction resulting from numerous causes.

Clinical manifestations include symptoms of respiratory distress and frequent findings of a third heart sound and hepatomegaly from heart failure. X-ray studies show cardiomegaly with occasional pulmonary venous congestion and an electrocardiogram shows ST-T segment flattening and inversion (leads I, aV_L and left precordial leads) and occasionally an abnormal axis or dysrhythmias. About half show left ventricular hypertrophy as well. Echocardiography and cardiac catheterization exclude other abnormalities and show poor cardiac function and abnormal left ventricular volumes.

Pathologically there may be evidence of acute or chronic myocarditis, various degrees of hypertrophy and fibrosis or endocardial fibroelastosis; occasionally specific infiltrates are seen. In pathophysiologic terms dilated cardiomyopathy is seen most often, hypertrophic cardiomyopathy is next and restrictive cardiomyopathies are rare. The etiology of most myocardial disease is unknown, but many specific causes are known and should be sought vigorously. Myocardial disease may be associated with collagen disease, hypertension, neuromuscular disease (Friedreich's ataxia), infiltrative (Pompe's) disease or specific infections (coxsackievirus, mononucleosis) or be drug induced (anthracyclines irradiation) or associated with systemic deficiency states (carnitine, selenium). It is recommended that plasma carnitine and selenium levels be determined in any patient with cardiomyopathy and that a skeletal muscle biopsy be done in any patient with known familial cardiomyopathy.

All patients who have myocardial disease may benefit from symptomatic and supportive treatment—oxygen, bed rest and administration of digitalis and diuretics. Those with a specific treatable cause such as carnitine and selenium deficiency respond dramatically to replacement therapy. Myocardial disease due to anthracycline chemotherapy is usually avoidable if a maximum dose of 500 mg per sq m of body surface area is not exceeded. Recovery is frequently rapid after discontinuance of therapy.

Patients with idiopathic myocardial disease may recover completely, survive with residual cardiac dysfunction or die from their disease, all in approximately equal proportions. Factors that when present initially predict an ominous outcome are pulmonary vascular congestion, a cardiac index of less than 3 liters per minute per sq m and a northwest (right and superior) axis on electrocardiogram. The presence of heart failure, dysrhythmias, left ventricular hypertrophy or age at onset do not alter the outcome.

Those patients with identifiable causes may have a varied outcome. Some types of myocardial disease, such as glycogenosis or neuromuscular disease, are progressive and fatal. Patients with infections frequently recover. The knowledge that patients with carnitine and selenium deficiency may recover fully supports aggressive diagnostic efforts. Echocardiography is an excellent tool for sequentially following cardiac function regardless of the cause.

Hypertrophic cardiomyopathy is a form of myocardial disease characterized by a hypertrophied nondilated left ventricle with disproportionate thickness of septum compared with free wall. Nonspecific ejection murmurs are usually heard and patients may have no symptoms, cardiomegaly or heart failure. Diagnosis is made by echocardiography and catheterization. Treatment with drugs such as propranolol hydrochloride or verapamil frequently produces improvement; severe obstruction may be treated by myotomy-myectomy. A transient form of hypertrophic cardiomyopathy is seen in infants of diabetic mothers and usually requires no treatment.

(Greenwood RD: Diagnosis and treatment of myocardial disease in infants and children [Information]. West J Med 1984, Nov; 141:698)

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In Memoriam

California Medical Association

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CHIMIKLIS, ARTHUR G., Stockton. Died June 23, 1984, in Stockton of cancer, aged 68. Graduate of Harvard Medical School, Boston, 1944. Licensed in California in 1950. Dr Chimiklis was a retired member of the San Joaquin County Medical Society.

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CITRET, COLEMAN, San Francisco. Died June 16, 1984, in San Francisco of heart disease, aged 67. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1941. Licensed in California in 1950. Dr Citret was a member of the San Francisco Medical Society.

❦

CONDIT, PHILIP K., Oakland. Died August 18, 1984, in Oakland, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr Condit was a retired member of the Alameda-Contra Costa Medical Association.

❦

CUTLER, MAX, Camarillo. Died July 6, 1984, in Camarillo, aged 85. Graduate of Johns Hopkins School of Medicine, Baltimore, 1922. Licensed in California in 1949. Dr Cutler was a retired member of the Los Angeles County Medical Association.

❦

DUVIGNEAUD, DESALES, San Diego. Died in May 1984, aged 70. Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1939. Dr DuVigneaud was a retired member of the San Diego County Medical Society.

❦

FELLOW, DONALD J., Watsonville. Died May 20, 1984, in Loma Linda, aged 56. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1955. Licensed in California in 1956. Dr Fellow was a member of the Santa Cruz Medical Society.

❦

GOTTLIEB, FREDERICK I., Walnut Creek. Died July 10, 1984, in Walnut Creek of myocardial infarct, aged 62. Graduate of Emory University School of Medicine, Atlanta, 1947. Licensed in California in 1955. Dr Gottlieb was a retired member of the Alameda-Contra Costa Medical Association.

❦

LOCKE, ALEXANDER, Sacramento. Died June 26, 1984, in Sacramento of leukemia, aged 52. Graduate of the Marquette University School of Medicine, Milwaukee, 1967. Licensed in California in 1972. Dr Locke was a member of the Sacramento-El Dorado Medical Society.

LOEHNER, CONRAD A., Upland. Died March 27, 1984, in Upland of cerebrovascular accident, aged 83. Graduate of Columbia University College of Physicians and Surgeons, New York, 1933. Licensed in California in 1940. Dr Loehner was a retired member of the San Bernardino County Medical Society.

❦

LOGAN, GEORGE W., Newport Beach. Died March 28, 1984, of lung cancer, aged 54. Graduate of Baylor University College of Medicine, Houston, 1954. Licensed in California in 1960. Dr Logan was a retired member of the Orange County Medical Association.

❦

MCCAUSLAND, JOHN, Chula Vista. Died June 23, 1984, in Chula Vista, aged 72. Graduate of Washington University School of Medicine, St Louis, 1937. Licensed in California in 1937. Dr McCausland was a retired member of the San Diego County Medical Society.

❦

MANKIN, DOROTHEA R., Chula Vista. Died July 25, 1984, aged 69. Graduate of Bowman Gray School of Medicine, Winston-Salem, NC, 1946. Licensed in California in 1955. Dr Mankin was a member of the San Diego County Medical Society.

❦

O'SHEA, WILLIAM A., Petaluma. Died June 25, 1984, in Petaluma, aged 58. Graduate of Boston University School of Medicine, 1949. Licensed in California in 1957. Dr O'Shea was a member of the Sonoma County Medical Association.

❦

ROGERS, MAURICE B., Sherman Oaks. Died January 27, 1984, aged 78. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1934. Dr Rogers was a retired member of the Los Angeles County Medical Association.

❦

ROOT, AMOS B., JR, San Diego. Died May 31, 1984, in San Diego, aged 65. Graduate of the University of Southern California School of Medicine, Los Angeles, 1944. Licensed in California in 1946. Dr Root was a member of the San Diego County Medical Society.

❦

ROSENZWEIG, SAMUEL E., San Diego. Died May 16, 1984, in San Diego of myocardial infarct, aged 50. Graduate of the University of Rochester School of Medicine and Dentistry, 1959. Licensed in California in 1965. Dr Rosenzweig was a member of the San Diego County Medical Society.

❦

SANDS, RUSSELL, Palm Springs. Died June 14, 1984, in Palm Springs, aged 91. Graduate of Oakland College of Medicine and Surgery, Oakland, Calif, 1920. Licensed in California in 1920. Dr Sands was an associate member of the Los Angeles County Medical Association.

SAWYER, LESTER J., San Francisco. Died July 7, 1984, in Palo Alto, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1936. Dr Sawyer was a retired member of the San Francisco Medical Society.

❦

SCHMID, FREDERIC W., San Francisco. Died May 16, 1984, in San Francisco of myocardial infarct, aged 66. Graduate of Universität Heidelberg Medizinische Fakultät, Germany, 1950. Licensed in California in 1955. Dr Schmid was a member of the San Francisco Medical Society.

❦

SHEIFFER, JEROME E., Inglewood. Died May 24, 1984, aged 50. Graduate of Tufts University School of Medicine, Boston, 1959. Licensed in California in 1964. Dr Sheiffer was a member of the Los Angeles County Medical Association.

❦

TAYLOR, WESLEY H., Redwood City. Died August 15, 1984, in Palo Alto, aged 82. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1930. MD degree from California College of Medicine, 1962. Dr Taylor was a member of the San Mateo County Medical Society.

❦

TUCKER, IRENAEUS, N., San Rafael. Died August 6, 1984, in San Rafael of heart disease, aged 63. Graduate of Tulane University School of Medicine, New Orleans, 1945. Licensed in California in 1951. Dr Tucker was a retired member of the Marin Medical Society.

❦

WEISS, ISIDORE IRWIN, Stockton. Died June 8, 1984, in Stockton, aged 77. Graduate of Faculty of Medicine, University of Edinburgh, 1931. Licensed in California in 1937. Dr Weiss was a retired member of the San Joaquin County Medical Society.

❦

WHITE, WENDELL WILLIAM, Perris. Died May 14, 1984, in Perris, aged 76. Graduate of the University of Oregon Medical School, Portland, 1939. Licensed in California in 1940. Dr White was a member of the Riverside County Medical Association.

❦

WILSON, JOHN CREE, JR, Los Angeles. Died July 2, 1984, of heart disease, aged 63. Graduate of Harvard Medical School, Boston, 1944. Licensed in California in 1946. Dr Wilson was a member of the Los Angeles County Medical Association.

❦

WINEBERG, ANAH, Oakland. Died May 29, 1984, aged 86. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Dr Wineberg was a retired member of the Alameda-Contra Costa Medical Association.

❦

New Mexico Medical Society

MORTIMER, HAROLD M., Albuquerque. Died August 23, 1984, in Albuquerque, aged 83. Graduate of the University of Illinois College of Medicine, Chicago, 1929. Licensed in New Mexico in 1933. Dr Mortimer was a retired member of the San Miguel County Medical Society.

TENNEY, ALONZO C., Albuquerque. Died August 3, 1984, aged 75. Graduate of the University of Illinois College of Medicine, Chicago, 1946. Licensed in New Mexico in 1961. Dr Tenney was an emeritus member of the Albuquerque & Bernalillo Medical Society.

❦

Washington State Medical Association

BITTNER, JOS ERIC, JR, Yakima. Died February 28, 1984, aged 87. Graduate of Northwestern University Medical School, Chicago, 1925. Licensed in Washington in 1925. Dr Bittner was a retired member of the Yakima County Medical Society.

❦

CLARK, JOHN ANGUS, Seattle. Died July 23, 1984, aged 75. Graduate of Western Reserve University School of Medicine, Cleveland, Ohio, 1935. Licensed in Washington in 1939. Dr Clark was a retired member of the King County Medical Society.

❦

COCHRAN, WERDNA F., Richland, Wash. Died July 18, 1984, in Shanghai of myocardial infarct, aged 59. Graduate of Loma Linda University School of Medicine, 1970. Licensed in Washington in 1970. Dr Cochran was a member of the Benton-Franklin County Medical Society.

❦

EVOY, MATTHEW H., Seattle. Died August 13, 1984, in Seattle, aged 72. Graduate of St Louis University School of Medicine, 1942. Licensed in Washington in 1942. Dr Evoy was a member of the King County Medical Society.

❦

GREGSON, AMOS M., Pasco. Died August 9, 1984, aged 73. Graduate of the University of Oregon Medical School, Portland, 1952. Licensed in Washington in 1954. Dr Gregson was a retired member of the Benton-Franklin County Medical Society.

❦

LAVIZZO, BLANCHE S., Seattle. Died August 28, 1984, aged 59. Graduate of Meharry Medical College, Nashville, 1950. Licensed in Washington in 1952. Dr Lavizzo was a member of the King County Medical Society.

❦

MORTON, ROBERT JAMES, Seattle. Died July 28, 1984, aged 67. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1943. Licensed in Washington in 1946. Dr Morton was a member of the King County Medical Society.

❦

STEPHAN, ALLEN H., Bremerton. Died August 13, 1984, aged 54. Graduate of the University of Michigan Medical School, Ann Arbor, 1962. Licensed in Washington in 1967. Dr Stephan was a member of the Kitsap County Medical Society.

❦

Wyoming Medical Society

ZUCKERMAN, SAM S., Cheyenne. Died September 18, 1984, in Cheyenne, aged 84. Graduate of the University of Colorado School of Medicine, Denver, 1934. Licensed in Wyoming in 1934. Dr Zuckerman was a retired member of the Laramie County Medical Society.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure, certain conduction defects, angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL. In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC. Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetics).

PHARMACOKINETIC. A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 vs. 1,024 ng/ml·hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General. Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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Cardiology with invasive vascular procedures	4,849
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Colon Rectal Surgery	6,997
Dermatology — no radiation or hair transplants	2,377
Gastroenterology with endoscopy and ERCP, board certified	3,613
Family Practice — no surgery	2,377
Family Practice — minor surgery or assisting at surgery	3,613
Family Practice — major surgery	7,908
Gynecologic Surgery	7,908
Internal Medicine with invasive vascular procedures	4,849
Internal Medicine — no invasive vascular procedures	2,377
Neurology	1,141
Ophthalmology with surgery or laser	3,613
Orthopedics with spinal surgery/chemonucleolysis	9,731
Orthopedics — no spinal surgery or chemonucleolysis	8,820
Orthopedics — restricted to hand surgery	7,908
Otolaryngology— doing plastic surgery, board certified	7,908
Pediatrics — General	1,141
Pediatrics — General, with invasive vascular procedures	4,849
Pediatric Cardiology — no invasive vascular procedures	2,377
Pediatric Cardiology — with invasive vascular procedures	4,849
Plastic Surgery, board certified	7,908
Psychiatry — no electro-convulsive therapy	1,141
Pulmonary Medicine — with flexible bronchoscopy	2,377
Radiology — reading films only	1,141
Radiology — diagnostic, no coronary angiography	2,377
Radiology — including coronary angiography	4,849
Radiology — therapeutic	4,849
Urology	6,085

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(Continued from Page 606)

RADIOLOGY

December 8—**Gastrointestinal Radiology.** Cedars-Sinai Medical Center at Los Angeles. Saturday. Contact: Lore Kahane, PO Box 48750, Room 2049, Los Angeles 90048. (213) 855-5547.

February 27-March 1—**5th Annual Approaches: Radiologic, Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: UCSF.

SPORTS MEDICINE

January 13-17—**Sports Medicine: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: UCD.

January 26—**Nutrition for Athletic Performance.** American Heart Association at University of California at Berkeley, Berkeley. Saturday. 4 hrs. Fee: $40. Contact: American Heart Association, PO Box 5157, Oakland 94605. (415) 632-9606.

SURGERY

November 28-December 2—**Basic Microsurgery Training Workshop.** UCSD. Wednesday-Sunday.

November 30-December 2—**Bone Grafting for Maxillofacial Indications.** Plastic Surgery Research Foundation at Hotel Intercontinental, San Diego. Friday-Sunday. $295.

December 1-8—**Temporal Bone Surgical Dissection—1984.** House Ear Institute at Los Angeles. 62 hrs. One week. Contact: Antonio de la Cruz, MD, Director of Education, HEI, 256 South Lake St., Los Angeles 90057. (213) 483-4431

December 3-5—**Current Trends in Total Knee Arthoplasty.** American Academy of Orthopaedic Surgeons at Lake Tahoe. Monday-Wednesday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

December 3-7—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs.

December 6-9—**The Adult Hip.** American Academy of Orthopaedic Surgeons at Rancho Mirage. Thursday-Sunday. Contact: AAOS, 444 N. Michigan Ave., Chicago, IL 60611.

December 12—**Orthopedic Surgery-Arthroscopy—Diagnosis and Treatment.** LLU. Wednesday.

December 13-16—**Acetabular and Lower Extremity Fracture Management Symposium.** UCD at Caesars Tahoe, South Lake Tahoe. Thursday-Saturday. 21 hrs. Fee: $475. Contact: UCD.

December 14—**A Modern Look at Trauma.** Daniel Freeman Memorial Hospital, Inglewood. Friday. 6 hrs. Contact: DFMH, Dept. of Medical Education. (213) 674-7050, Ext. 3427.

January 14-18—**Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

January 18-19—**7th Annual Postgraduate Course in Surgery.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday. Contact: UCD.

January 21-25—**8th Annual San Diego Postgraduate Assembly in Surgery.** UCSD. Monday-Friday. Contact: UCSD.

February 11-15—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

OF INTEREST TO ALL PHYSICIANS

November 18—**16th Annual Symposium; "The Newest Concepts in Clinical Practice."** Granada Hills Community Hospital & UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Carol Smith, Granada Hills. (818) 360-1021.

November 30-December 2—**Weekend Workshops on Stress for Women Physicians—Partners Welcome.** CMA at La Playa Hotel, Carmel. Friday-Sunday. Contact: Sandy Willett, CMA, (415) 863-5522, Ext. 418.

December 31—**4th Annual Potpourri of Medicine Seminar.** Huntington Memorial Hospital, Pasadena. Monday. 6 hrs. $110. Contact: Med. Staff Coord., Huntington Memorial Hospital, 100 Congress St., Pasadena 91105. (818) 440-5165.

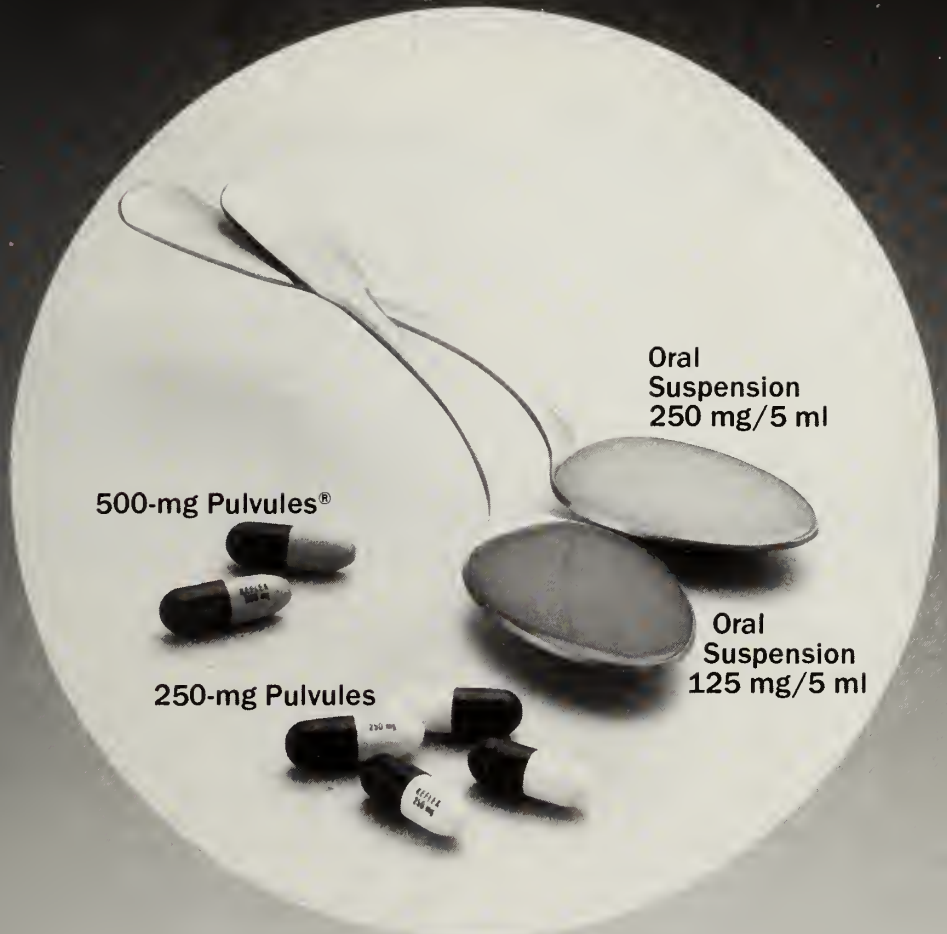
January 14-18—**Intensive Course in Geriatric Medicine.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Monday-Friday. 33.75 hrs. Fee: $410.

January 20-23—**54th Annual Midwinter Clinical Conference.** Research Study Club of Los Angeles at Los Angeles Hilton Hotel. Sunday-Wednesday. 24 hrs. Contact: Louise Ball, Executive Secretary, PO Box 1464, South Pasadena 91030.

January 23-26—**Annual Review in Family Medicine:**

(Continued on Page 706)

Easy To Take



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(Continued from Page 704)

Controversies and Challenges in Primary Care. Sir Francis Drake Hotel, San Francisco. Wednesday-Saturday.

January 31-February 2—**Recent Advances in Geriatric Medicine: Dementia in the Elderly.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thursday-Saturday. 13 hrs. $210.

February 6-8—**Neurology for Non-Neurologists.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 21 hrs. Contact: UCSD.

February 11-16—**UCI Family Practice Refresher Course.** UCI at Newport Beach Sheraton Hotel. Monday-Friday. 58 hrs. Contact: UCI.

February 11-22—**Intensive Residency on Occupational Medicine.** UCSF at San Francisco. Two weeks. 80 hrs. Fee: $1,000. Contact: UCSF.

February 13-15—**Clinical Laboratory Molecular Analysis: Future Direction.** Scripps Clinic and Research Foundation at Vacation Village San Diego. 21 hrs. Contact: Dianne Tisue, Scripps Clinic, 10666 North Pines Rd, La Jolla 92037. (619) 457-8556.

February 22-23—**American College of Physicians: 1985 Regional Scientific CME Meeting.** ACP at Doubletree Inn, Monterey. Friday-Saturday. Contact: Jerry P. Lewis, MD, 618 Francisco Place, Davis 95616.

February 23-24—**Expanding Horizons.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF.

March 1—**11th Annual Diabetes Program.** UCD. Friday.

March 6-8—**35th Annual Course for Physicians in Family Practice.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin Jackson, Office of Continuing Education, PO Box 7921, San Francisco 94115. (415) 885-7269.

March 29-31—**Office Emergencies in Primary Care.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee; $275. Contact: Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

IDAHO

February 16-23—**Internal Medicine.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 23-March 2—**Office Orthopaedics.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 2-9—**Electromyography.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

February 20-23—**Big Sky Pulmonary/Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Contact: ALA of Montana, 825 Helena Ave., Helena 59601. (406) 442-6556.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chariman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 15-16—**ABC's of Chronic Lung Disease in Infants, Children and Young Adults.** Albuquerque. Thursday-Friday. 17 hrs. AMA Cat. I. Contact: Winrock Medical Plaza Pediatric Pulmonary Center, 7400 Indian School Rd. NE, Albuquerque 87110. (505) 883-8217.

November 29-30—**Update on Alzheimer's Disease.** Albuquerque. Thursday-Friday. 6 hrs. NM Required Education, Cat. I. Contact: Pat Graves, American Geriatrics and Gerontology Association, 1024 Eubank NE, #A, Albuquerque 87111. (505) 292-0415.

(Continued on Page 708)

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(Continued from Page 706)

November 30-December 1—Trauma Update 84. Albuquerque. Friday-Saturday. Albuquerque Convention Center/Regent Hotel. 11 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

January 12-13—**3rd Annual Albuquerque Family Practice Seminar—Medical Issues in Gerontology.** Albuquerque. Saturday-Sunday. Marriott Hotel. 13 hrs. AMA Cat. I, AAFP Prescribed. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

January 23-27—**New Mexico Metabolism Symposium.** Taos. Wednesday-Sunday. Tennis Ranch. 12 hrs. AMA Cat. I. Contact: Office of CME, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87106. (505) 262-7353.

February 1-3—**Advances in Internal Medicine V.** Albuquerque. Friday-Sunday. 15 hrs. AMA Cat. I. Veterans Administration Medical Center. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

February 21-23—**18th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

March 15-16—**Primary Care Orthopaedics.** Albuquerque. Friday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

April 11-13—**Seventh Annual Pediatric Cardio-Pulmonary Update.** Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phome (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued on Page 721)

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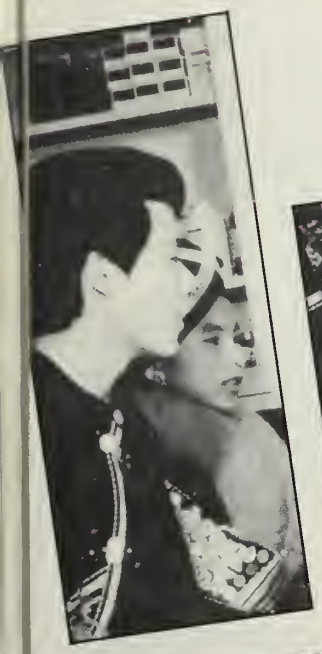

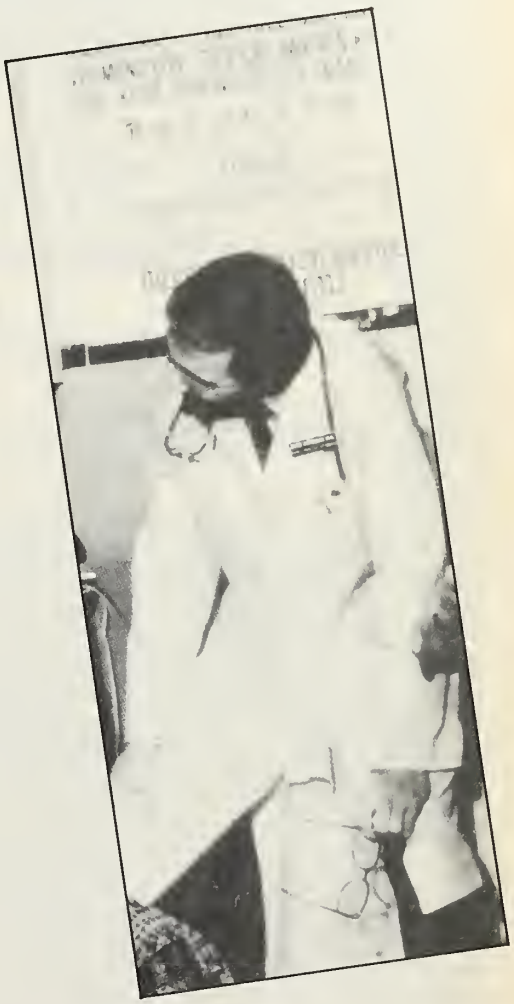

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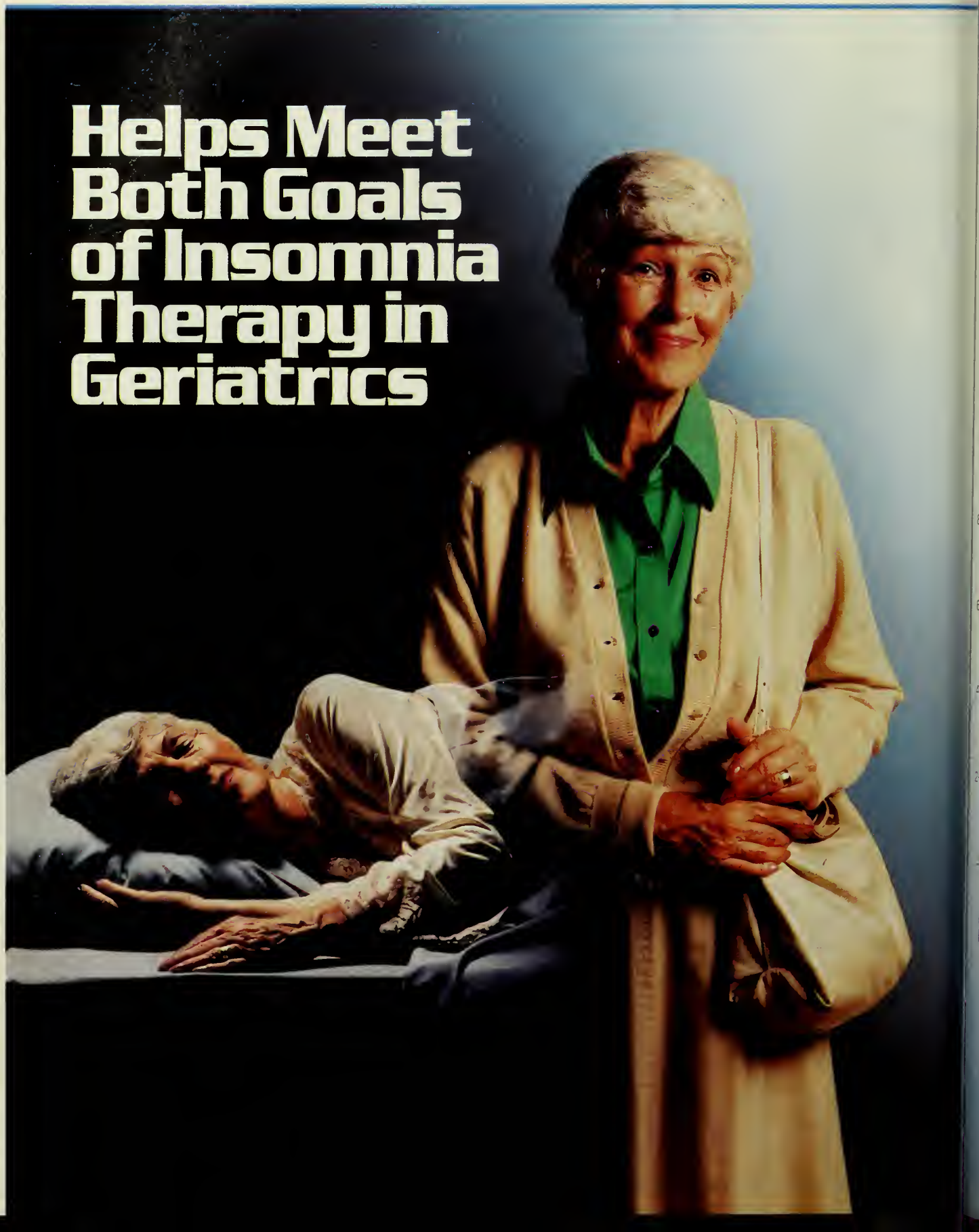
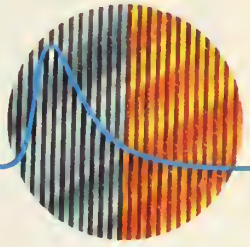
triazolam (IV)



Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

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- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
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Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

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Halcion
triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

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Halcion Tablets
triazolam C-IV

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam C-IV

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 1983

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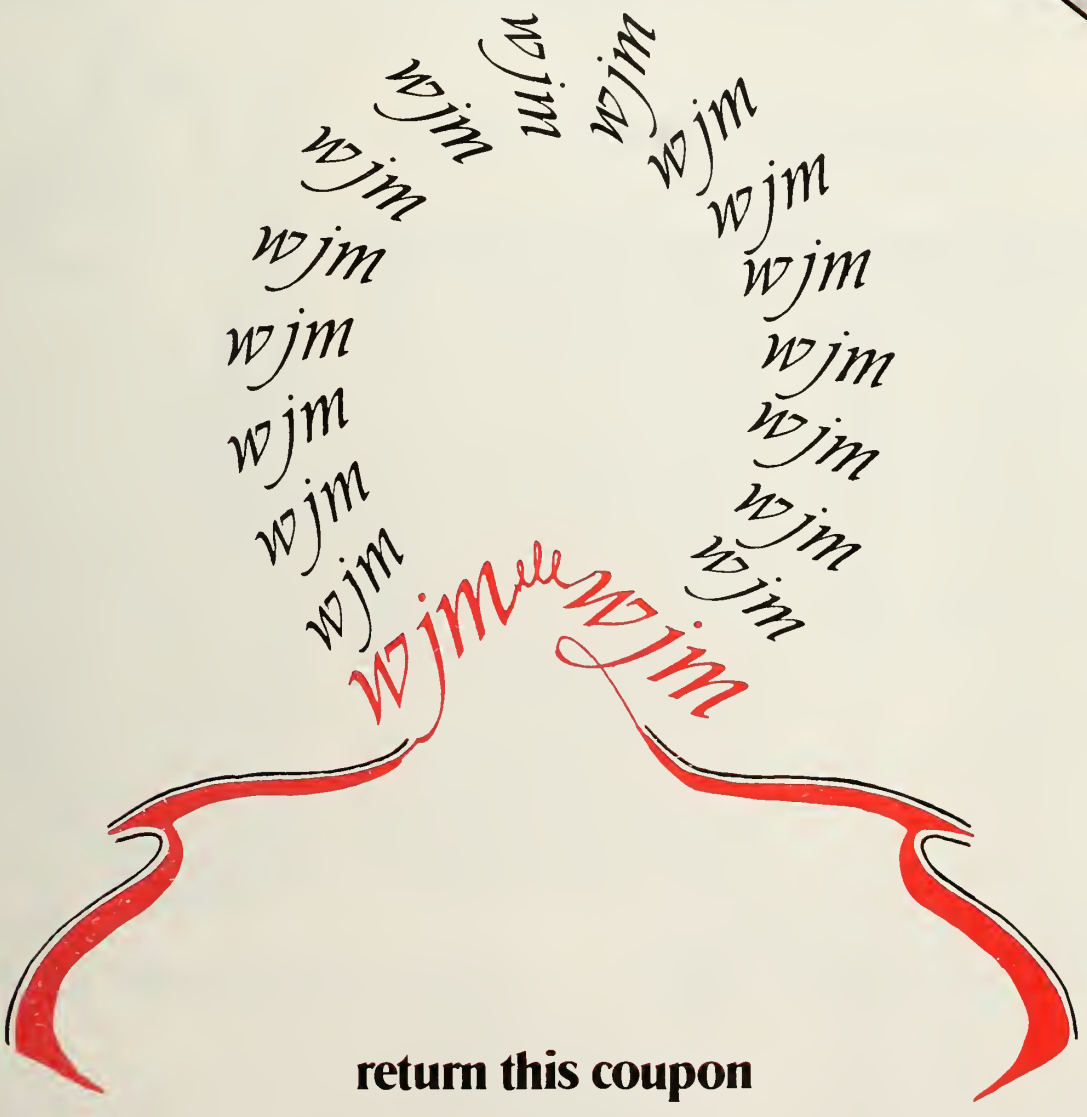

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OBSTETRICIAN AND GYNECOLOGIST, Southern California—Leading HMO with 28 facilities, 350,000 members and 370 full-time physicians in Los Angeles and Orange Counties has opportunities for OB/GYN specialists. Excellent compensation and benefits. Send curriculum vitae to Director/Physician Recruitment: CIGNA Healthplans of California, 700 N. Brand Blvd , Suite 500, Glendale, CA 91203.

CALIFORNIA-URGENT CARE. Positions available for Fall 1984 in free-standing, urgent care settings in several locations. Board certification or eligibility in Emergency Medicine, Family Practice or related specialty required. Opportunities exist for directorships for physicians with appropriate experience. Guaranteed minimum, malpractice paid, benefit package available. Contact: California Emergency Physicians, 440 Grand Ave, Suite 500, Oakland, CA 94610, (415) 832-6400.

FAMILY PRACTICE OPPORTUNITY. Established Family Practice group located in SW Washington, 15 minutes from Portland. Flexible scheduling Full partnership available within one year. Contact E. M. McAninch, MD at (206) 834-3141 or send CV to P.O. Box 1004, Camas, WA 98607.

LA JOLLA, CALIFORNIA-PULMONOLOGIST needed to join pulmonary-critical care group. Salary and later partnership or early buy-in. Must be BE/BC. Send CV to Box 6444, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

UNIVERSITY OF WYOMING STUDENT HEALTH SERVICE—The Student Health Service has an opening for a full-time physician beginning July 1, 1984. The physician must be Board Certified in Family Practice and have approved resident training or have extensive practice experience. Applicant must be licensed in the State of Wyoming and have at least four years of primary care experience. Physician to join three full-time and three part-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, pharmacy and infirmary. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity-Affirmative Action Employer. Send CV to: Dale C. Brentlinger, MD, Director, Student Health Service, University of Wyoming, University Station Box 3068, Laramie, Wyoming 82071.

GENERAL PRACTITIONERS—Specialists—Full-time positions or Locum Tenens. If you're considering a change—let's talk. We have opportunities in California and other West Coast areas. Send your CV to: Physician Search Associates Agency Inc., 1835 Orangewood Ave., Suite 306, Orange, CA 92668.

FAMILY PRACTITIONER/EMERGENCY PHYSICIAN: MD multispecialty group is seeking second MD to staff urgent care clinic. Partnership potential. Board qualified in Family Practice/Emergency Medicine. Beautiful coastal location. Send CV to James Beckett, MD, Santa Cruz Medical Clinic, 2025 Soquel Avenue, Santa Cruz, CA 95062.

PHYSICIANS WANTED

ORTHOPEDIC SURGEON, Sun Valley, Idaho. Energetic Orthopedic Surgeon to practice with multi-specialty group. Well equipped adjacent hospital. Ouality of life high, income moderate. Curriculum vitae and references with first letter please. Dr Lynn T. Levy, PO Box 66, Sun Valley, ID 83353.

FELLOWSHIP IN GENERAL INTERNAL MEDICINE—UCSF/San Francisco General Hospital. Two year program emphasizing clinical research, teaching, patient care and management skills. Available July 1985. Applicants must be Board eligible. Contact Richard J. Haber, MD, Chief, Division of General Internal Medicine 5H22, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110.

FAMILY PHYSICIAN—Board certified or eligible to join the Family Practice Dept. of a growing primary care based, multispecialty group in Northwest Washington. Close to CME and outdoor recreation. Contact Shane Spray, Administrator, Skagit Valley Medical Center, Mt. Vernon, WA 98273; (206) 428-2524.

OCCUPATIONAL PHYSICIAN: Occupational Medicine physician desired for hospital and community based occupational health program. Hospital with over 1,400 employees is located in a medium-sized, highly industrial area in the Northwest that offers excellent schools, recreational and cultural opportunities. Must have clinical skills and administrative experience. Salary based upon experience and qualifications. Contact Ambulatory Care Services, PO Box 2197, Tacoma, WA 98401 or (206) 591-6709.

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OB/GYN—TULARE COUNTY, CALIFORNIA: Board certified/eligible OB/GYN to practice in an outpatient clinic with 13 physicians. Consider a rural lifestyle with cultural amenities of metropolitan areas, Los Angeles and San Francisco easily accessed and the Sierra Nevada Mountains nearby. Salary: $85,376-$89,725 annually. The County provides a benefit package which includes malpractice insurance coverage. Send CV to: Tulare County Personnel, Courthouse, Room 106, Visalia, CA 93291, (209) 733-6266. An affirmative action employer.

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BOARD ELIGIBLE/CERTIFIED SURGEON being recruited by physicians and community to serve the needs of a rural area in beautiful northeastern Washington. Service area of approximately 15,000, solid family practice referral base, sole community hospital/nursing home located in the county seat of Newport, 40 miles north of Spokane. Enjoy the benefits of living year around in a vacationer's paradise, professional satisfaction and the challenge of providing much needed surgical services. Tertiary referral and cross coverage available. Contact David D. Buckman, MD, Chief of Staff or John B. Switzer, Administrator, Newport Community Hospital, Newport, WA 99156.

GASTROENTEROLOGIST: BC or BE, to associate with 4 man internal medicine group in small Northern California city. Modern, complete, endoscopy lab at local hospital. Salary plus percentage. Early partnership, Please send CV to Box 6449, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

A LARGE MULTISPECIALTY REFERRAL CENTER in downtown Seattle will be establishing a major satellite clinic in Federal Way, located 25 miles from the main campus. Well qualified, Board certified or Board eligible physicians in Primary Care areas are encouraged to apply. Send curriculum vitae to: Health Services Consortium, 925 Seneca St., PO Box 1930, Seattle, WA 98111.

FAMILY PRACTICE—Excellent opportunity in New Mexico and Colorado communities for private practice with income quarantee. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

INTERNAL MEDICINE—Excellent opportunity in New Mexico and Colorado communities for private practice with income guarantee. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

WESTERN US, OPENINGS—Several multi-specialty groups and clinics have asked us to recruit physicians for over 50 positions of various specialties. Western States Professional Services, 1551 E. Shaw, #115, Fresno, CA 93710, (209) 226-3363.

(Continued on Page 716)

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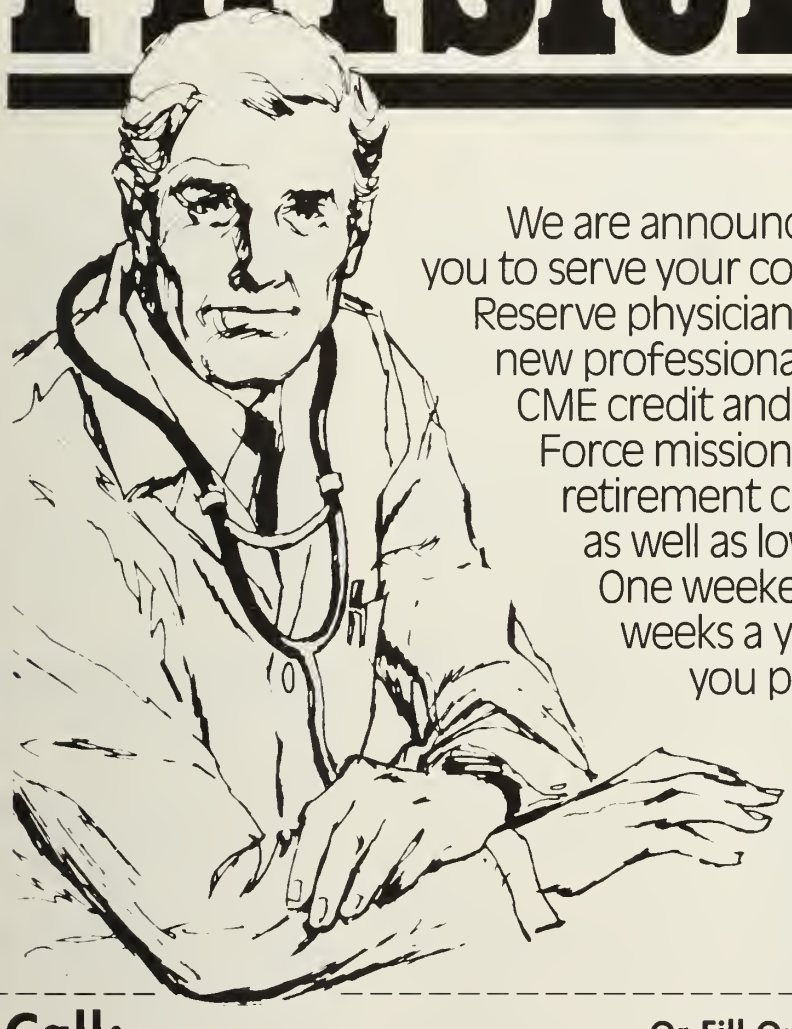

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(Continued from Page 714)

INTERNIST-GP/OB-GYN/FP/GP/RADIOLOGIST: For established growing, multi-specialty practice in sunny Los Angeles. Spanish very helpful. First year compensation negotiable. Partnership potential second year. CV to Medical Director, Box 6435, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE: Fellowship in Obstetrics and Family Medicine available July 1, 1985 to June 30, 1986 for qualified FP residency graduate. Opportunity to learn complicated and operative OB while teaching FP residents in beautiful Pacific Northwest. University of Washington faculty appointment, salary and fringes. Send letter and CV: Philip Cleveland, MD, Director, Family Medicine Spokane, S. 511 Pine St., Spokane, WA 99202, (509) 642-2313.

FAMILY PRACTITIONER needed to work as independent contractor on the Monterey Peninsula. Please reply to: Marc Martinez, MD, 8410 Galaxy Circle, Buena Park, CA 90620, (714) 761-3419 or (415) 924-2566.

FAMILY PRACTITIONER—Exceptional opportunity to join five man clinic adjacent to 55 bed acute care hospital. Rural setting in Northern Sacramento Valley. 1 hour from Sacramento, 2 hours from San Francisco and Lake Tahoe. Apply immediately. Send CV to Albert W. Nielsen, MD, Gridley Medical Group, 225 Spruce St., Gridley, CA 95948, (916) 846-5655.

CARDIOLOGIST—Needed now in Southern California, Board certified or eligible to join expanding group. Excellent compensation package. Please send CV to Box 6452, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PATHOLOGIST—The Glennview Pathology Medical Group, with affiliations at six hospitals in the greater Los Angeles area, is looking for a competent Pathologist certified in anatomic and clinical pathology. Applicants should have a desire to grow with the Group, be competent in surgical pathology and interested and able in clinical pathology. Send résumé to: Glenview Pathology Medical Group, 4374 Overland Avenue, Culver City, CA 90230.

OB/GYN: Multi-specialty group in Northwest Washington desires second obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 East Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

ONCOLOGIST/INTERNIST: BC/BE to join eighteen physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 East Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

OTOLARYNGOLOGIST: BC/BE and also interested in facial plastics to join eighteen physician primary care and multispecialty group practice in beautiful Pacific Northwest setting. Reply to Shane Spray, 1400 East Kincaid, Mount Vernon, WA 98273, (206) 428-2524.

OB/GYN for excellent position in San Francisco Bay Area. Multi-specialty group. Contact: Carol Sweig, Western Physicians Registry, 1124 Ballena, Alameda, CA 94501, (415) 521-4110.

ORTHOPEDIC SURGEON for excellent position in San Francisco Bay Area. Multi-specialty group. Contact: Carol Sweig, Western Physicians Registry, 1124 Ballena, Alameda, CA 94501, (415) 521-4110.

ANTERIOR SEGMENT FELLOWSHIP in busy private practice associated with Medical College. Intraocular Lens Implantation, including posterior chamber and anterior chamber lenses. Extracapsular and Phacoemulsification techniques. Argon and Yag Laser. Excellent benefits plus fringes. Send CV and career objectives to: Box 6450, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

BOARD-ELIGIBLE GENERAL INTERNIST for 6-man multi-specialty group in southwestern Colorado. Call: (303) 247-2611 or send CV to Bonnie DuPuis, PO Box 2637, Durango, CO 81301.

SACRAMENTO: Full-time positions available for Board-prepared or Board-certified Emergency Physicians with established multi-hospital group practicing in the Sacramento Valley. Group organized as partnership with competitive salary and benefits. Malpractice paid. All hospitals with moderate volumes, many act as EMS base-stations. Send CV to Sacramento Emergency Medical Group, PO Box 214584, Sacramento, CA 95821.

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SOUTH DAKOTA: Expanding physician-owned group has opening for full-time career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436, or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

WYOMING: Residency-trained or Board-prepared physician (preferred) for busy emergency department. Physician-owned group with malpractice, disability, health insurance, profit sharing, etc. Excellent hunting, fishing, skiing, etc., nearby. Contact Donald Kougl, MD, (307) 632-1436, or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career oriented Emergency Physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436, or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

UNEXPECTED OPPORTUNITY FOR INTERNIST to associate with three busy internists in suburban community 20 minutes east of San Francisco. Reply with CV to Box 6443, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTITIONER, BC/BE. Full-time position available with community clinic in beautiful family area near San Francisco. Excellent benefits and working conditions. Call and OB included. Call Arturo Ray (415) 471-5907 or send CV to Tiburcio Vasquez Health Center, 33255 Ninth St., Union City, CA 94587.

FAMILY PRACTITIONER BC/BE needed for large multi-specialty clinic in San Francisco Bay area. Competitive salary first year, with excellent benefits. Eligible for full partnership after one year. Send résumé to Administrator, San Jose Medical Group, 45 South 17th St., San Jose, CA 95112.

PHYSICIANS

Albuquerque, New Mexico

Lovelace Medical Center is offering full-time positions in an expanding network of Urgent Care Centers for career oriented Physicians. Preference given to those trained in Emergency Medicine, Internal Medicine, Family Practice or Pediatrics and/or with 3 years experience and ACLS required, ATLS desired.

For further information, contact: Lovelace Medical Center, Human Resources Department, 5400 Gibson Blvd. S.E., Albuquerque, NM 87108.

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LOCUM TENENS

GENERAL RADIOLOGIST seeks ½-time position in South Bay (S.F.). Experienced in routine diagnostic studies plus industrial injury—acute care cases. Reply to Box 6442, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

LOCUM TENENS NEEDED—FP for busy practice with emphasis on Obstetrics. Needed for 4 months beginning December 1, 1984. Contact Judith Babcock, MD, 7935 216th St. S.W. Suite E, Edmonds, WA 98020; (206) 775-0681.

WORK PART TIME: Position available for Internist or GP with Internal Medicine experience to work at Primary Care Practice in Northern California Sierra foothills community of 25,000, 70 miles North of Sacramento. Share rotating practice with two other MD's; you work 1 week in 3. Out-patient and in-patient responsibilites in modern, fully equipped hospital. Minimum salary of $2,000/week plus incentives. Insurance and housing provided. Send CV and references to: David Lomba, Business Manager, 133 'A' Ascot Ct., Moraga, CA 94556.

PRACTICE WANTED

BOARD CERTIFIED RADIOLOGIST, 32, presently in aggressive hospital practice, wishes to purchase or associate in quality office practice in a coastal Northern California, Pacific Northwest or Bay area community. Call (714) 645-2393.

SITUATIONS WANTED

UCLA GRADUATE/UNM IMR3 available July 1985 for 5-10 physician Internal Medicine group practice in Northern California-Oregon. Interests in ICU and computers (publication accepted). Contact: Marc Gelman, MD, 2901 Euclid, #24D, Albuquerque, NM 87106.

PRACTICES AVAILABLE

DERMATOLOGY—Southern California, Practice for sale. Established practice in prestigious county. Gross $193K. Beautiful 1,500 sq. ft. suite. Full price $125K. Professional Practice Sales (714) 832-0230.

SAN FRANCISCO PARTNERSHIP: New primary care clinic fifteen minutes from the heart of downtown San Francisco seeks BE/BC Primary Care Physician. No buy-in, guaranteed base compensation and incentive, regular hours. Ideal for physician who wants private practice setting with strong management and financial support. Send CV to: Michael Goluska, MD, 2200 Sixth Ave., Suite 1200-BB, Seattle, WA 98121, (206) 624-6888.

CALIFORNIA NEAR SAN JOSE. active Family Practice, well equipped office to rent or buy; accredited hospital, plan retirement. Write Box 6424, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WELL ESTABLISHED FAMILY PRACTICE AND CLINIC FOR SALE. 1,600 square feet, well equipped with laboratory, x-ray and surgery. Will negotiate terms. Contact J. Erickson, MD, Box 44488, Tacoma, WA 98444.

WESTERN WASHINGTON—Private practices available in OB/GYN, Pulmonary, Internal Medicine and Family Practice. For details, contact Eloise Gusman, 1 (800) 535-7698 or send CV to 2800 Veterans Blvd., Suite 170, Metairie, LA 70002. Our service is completely confidential and offered at no cost or obligation.

CALIFORNIA—Radiology, Ophthalmology, Ob/Gyn, Family, Internal, Surgery, Occupational Med., Pediatric, Orthopedic, Psychiatry, Dermatology, others. Contact: Mary Bradshaw, Practice Broker/Recruiter, 21 Altamount, Orinda, CA 94563, (415) 376-0762.

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QUINTON 1849 TREADMILL, Hewlett Packard, 2 Channel radiotelemetry, ECG Monitor, VDT and Permanent Record, Lung Function Analyzer, Portable Defibrillator, Box 4191, Irvine, CA 92714.

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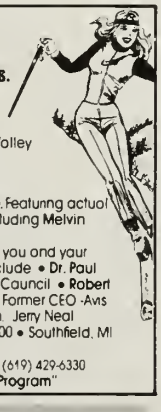

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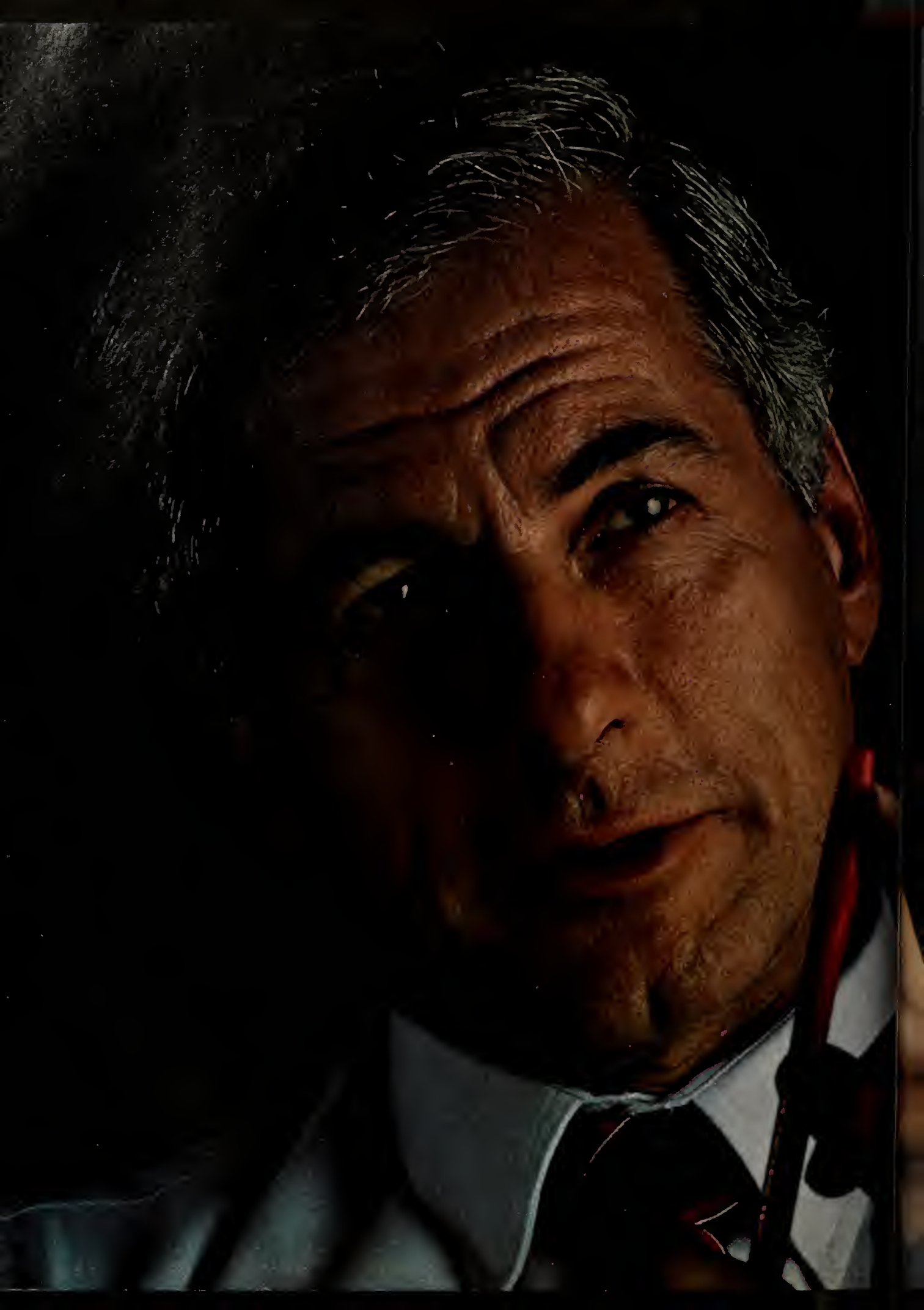

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Most doctors are pleasantly surprised to learn that the average cost of daily therapy with the world's most widely used beta blocker is so little, not much more than the cost of a daily newspaper.

When it's INDERAL tablets (propranolol hydrochloride) you want for your hypertension patients, remember to specify Dispense As Written (DAW) or Do Not Substitute on your prescriptions. That way, you can always be assured they'll get INDERAL®.

Please see next page for brief summary of prescribing information.

INDERAL®
(PROPRANOLOL HCl)
Small price to pay.

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10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure, certain conduction defects, angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL. In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC. Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing, at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC. A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 vs. 1,024 ng/ml•hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General. Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension, paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

•The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

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(Continued from Page 708)

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

DERMATOLOGY

March 20-21—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CMA.

EMERGENCY MEDICINE

November 15-16—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion-Jantzen Beach. Contact: OHSU-CME.

FAMILY PRACTICE

February 11-15—**Family Practice Review Program.** Portland. Monday-Tuesday. Marriott Hotel. Contact: OHSU-CME.

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

PATHOLOGY

March 20-21—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

SURGERY

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

November 30-December 1—**Soft Tissue Surgery.** Portland. Friday-Saturday. OHSU Campus. Contact: OHSU-CME.

February 10—**Alcohol and Drug Symposium.** Portland. Sunday. Marriott Hotel. Contact: OHSU-CME.

February 28-March 3—**Update in Rheumatology—1985.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME offce for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

November 30—**Sleep Disorders: A Clinical Approach** (Sponsor: University of Utah/Pulmonary Division, LDS Hospital). Friday. Marriott Hotel, Salt Lake City. Credit and fee to be announced. Contact: DuWayne Schmidt, MD, (801) 321-1100.

(Continued on Page 724)

When anxiety and organic disease are paired...

TROUBLED HEART

A

An obstructed coronary artery suggests the heart is already troubled—or soon will be. In most cases, the obstruction proves to be an atherosclerotic plaque. At other times—as in this case—the "blockage" stems largely from sudden spasmodic contractions of the arterial wall. In the photos shown here—taken during the catheterization of a cardiac patient—you can see an actual coronary artery spasm in progress: (A) the coronary artery as it is at baseline; (B) the spontaneous narrowing of the vessel (arrow) to a 75% obstruction; and (C) subsidence of the spasm after intracoronary nitroglycerin.

B

C

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ROCHE

TROUBLED PATIENT

Disturbed by anginal pain, worried about what *could* happen—the cardiac patient may go through periods when anxiety symptoms and apprehension threaten to become unmanageable. At such times, a short course of Valium (diazepam/Roche) can offer substantial relief of acute anxiety. Valium works promptly: Patients usually feel distinctly calmer in hours, report pronounced and sustained relief of anxiety within days. Helpful, too—adding an *h.s.* dose of Valium to the usual *t.i.d.* schedule can help relieve excessive nighttime anxiety.

An especially important benefit of Valium is that it is well tolerated by most cardiac patients. Side effects more serious than drowsiness, fatigue or ataxia are rare. Patients should be cautioned against drinking alcohol or driving while taking Valium. Periodic reassessment of the need for anxiolytic treatment is also recommended.

Unsurpassed in the treatment of anxiety symptoms

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scored tablets

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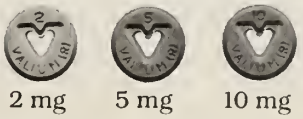

2 mg 5 mg 10 mg

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Please see summary of product information on following page.

Valium® (diazepam/Roche) Ⓥ
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not as sole therapy). The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.
***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.
Dosage: Individualize for maximum beneficial effect. *Adults.* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d., alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients.* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children.* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
How Supplied: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white, 5 mg, yellow, 10 mg, blue— bottles of 100 and 500, Prescription Paks of 50, available in trays of 10 Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.
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5 mg—5 VALIUM® (front) ROCHE (scored side)
10 mg—10 VALIUM® (front) ROCHE (scored side)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 721)

February 9-16—**8th Annual Update in Clinical Microbiology/Immunology** (Sponsor: University of Utah). Saturday-Saturday. Park City. Fee to be announced. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 12-15—**14th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 28 hrs. Contact: Linda Twitchell, (801) 581-8633.

February 17-20—**26th Annual Ob/Gyn Update** (Sponsor: University of Utah). Sunday-Wednesday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 20-23—**Reproductive Endocrinology and Infertility** (Sponsor: University of Utah). Wednesday-Saturday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 22-26—**30th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. Fee to be announced. 16 hrs. Contact: Vicky Larsen, (801) 581-6115.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

February 25-March 1—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 4-8—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 6-8—**Common Problems in Pediatrics VII** (Sponsor: University of Utah). Wednesday-Friday. Little America Hotel, Salt Lake City. Fee to be announced. 12 hrs. Contact: Wendy Ellis, (801) 363-1887 or Robert Bolte, MD, (801) 363-1221.

March 12-22—**Transport Workshop: Neonatal-Maternal-Administration** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 69½ hrs. Contact: Anne Shanahan, (801) 581-2730.

March 18-22—**5th Annual Nutrition in Contemporary Medicine Symposium** (Sponsor: University of Utah). Monday-Friday. Park City. Fee to be announced. 29 hrs. Contact: M. Rita Thomas, MD, (801) 581-3581.

March 21-23—**Practical Neurology for Clinicians** (Sponsor: University of Utah). Thursday-Saturday. Sheraton Hotel, Salt Lake City. Fee to be announced. 18 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 16—**Initial Management of Burn Patient.** Seattle. Friday. Riverton Hospital. Contact: U/W.

November 17-24—(HAWAII) **Medicine and Society in History.** One week. Inter-Continental Maui, Maui. Contact: U/W.

November 20—**Management of Thyroid Diseases.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

November 23-24—(HAWAII) **Father Damien's Leper Colony.** Molokai. Friday-Saturday. Sheraton Molokai. Contact: U/W.

November 30—**DX and Rx Syphilis.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 3-6—**DUR Counselors.** Bellevue. Monday-Thursday. Bellevue Hilton. Contact: U/W.

December 6—**Sleep Apnea-SIDS.** Seattle. Thursday. Children's Orthopedic Hospital. Contact: U/W.

December 6-7—**Aging and Elderly.** Seattle. Thursday-Friday. Westin. Contact: U/W.

December 7—**Practical Pediatrics.** Seattle. Friday. Contact: VMMC.

December 7—**Heart Catheterization.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 8—**Musculoskeletal Radiology.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

December 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

December 13-14—**Organ Failure and Organ Transplantation.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

December 14—**Ski Injuries.** Seattle. Friday. Riverton Hospital. Contact: U/W.

December 14—**Annual Strauss Lecture.** Seattle. Friday. UW Hogness Auditorium. Contact: U/W.

December 18—**Fever of Unknown Origin.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

December 26-January 2—(HAWAII) **Medicine, Magic and Religion.** Maui. Wednesday-Wednesday. Royal Lahaina. Contact: U/W.

December 28—**Diagnosis of Sleep Disorders.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 4—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 11—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 11—**Treatable Hepato-Biliary Disease.** Seattle. Friday. Contact: VMMC.

(Continued on Page 728)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111.(206) 223-6898.

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FRANCISC

(Continued from Page 725)

January 15—**General Topics in Hematology.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 18—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 23-25—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

January 24-26—**Annual President's Meeting—Modern Ophthalmic Technology.** Washington State Academy of Ophthalmology at Seattle. Thursday-Saturday. Westin. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

January 25—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 30—**Controversies in Medicine Circuit.** Vancouver. Wednesday. Contact: U/W.

January 31—**Controversies in Medicine Circuit.** Olympia. Thursday. Contact: U/W.

January 31-February 1—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin. Contact: U/W.

February 1—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 8—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 16—**Interventional Radiology to Abdomen.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

February 16-23—(IDAHO) **Internal Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 19—**Total and Home Parenteral Nutrition.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 20-22—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

February 22—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

February 23-March 2—(IDAHO) **Office Orthopaedics.** Sun Valley. Saturday- Saturday. Elkhorn Resort. Contact: U/W.

March 1—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 2-9—(HAWAII) **Medicine in China.** Kauai. Saturday-Saturday. Royal Waikola. Contact: U/W.

March 2-9—(IDAHO) **Electromyography.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 9-16—(HAWAII) **Imaging for Non-Radiologists.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 19—**Epilepsy.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

March 22—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 23—**Magnetic Resonance Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

March 23-30—(HAWAII) **Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 28-29—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences. Contact: U/W.

March 29—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 30-April 6—(HAWAII) **Neurology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 5—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 11-12—**DRG.** Seattle. Thursday-Friday. Westin. Contact: U/W.

April 12—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 13—**Handicapped Infant.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

(Continued on Page 731)

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Motrin is priced lower than Clinoril, Feldene, or Naprosyn.

The price of *Motrin* Tablets to pharmacies has been reduced as much as 35%. Patients taking the average dosage should now pay less for therapy with *Motrin* Tablets than for almost any other nonsteroidal anti-inflammatory drug you prescribe...less, for example, than for Clinoril, Feldene, or Naprosyn.

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Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia, **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit, **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription. MED B-7S

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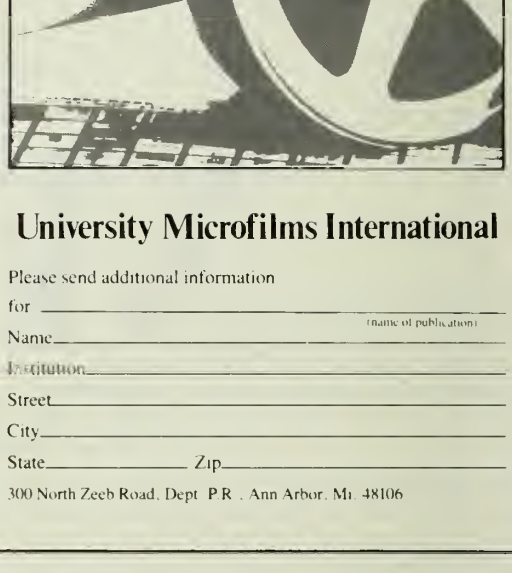

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The Western Journal of Medicine

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970; Section 3685, United States Code, for **THE WESTERN JOURNAL OF MEDICINE,** published monthly at San Francisco, California, for October, 1984.

1. Location of known office of publication: 44 Gough Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 44 Gough Street, San Francisco, California 94103.

3. Publisher: California Medical Association, 44 Gough Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 44 Gough Street, San Francisco; Managing Editor, David Greer, 44 Gough Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 44 Gough Street, San Francisco, California (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: There are no bondholders, mortgagees, or other security holders.

6. Paragraphs 4 and 5 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages or other securities of the publishing corporation have been included in paragraphs 4 and 5 when the interests of such individuals are equivalent to 1 percent or more of the total amount of the stock or securities of the publishing corporation.

7. Average number of copies each issue during preceding 12 months: Total 48,167, paid circulation by mail subscription, 47,005; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier or other means, 851; total distribution, 47,856; office use, leftover, unaccounted, spoiled after printing, 311; total net press run, 48,167. Single issue nearest to filing date, October, 1984: Total 48,500; paid circulation by mail subscription, 47,351; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier or other means, 829; total distribution, 48,180; office use, leftover, unaccounted, spoiled after printing, 320; total net press run, 48,500. David Greer, Managing Editor.

(Continued from Page 728)

April 16—**Ballard Hospital Lectures.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 17-19—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

April 18-19—**Death Investigation.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

April 19—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

April 26—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 26-27—**Sexual Assault.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

May 2-3—**Exercising Women.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 3—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 10—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 15-17—**Infectious Diseases.** Seattle. Wednesday-Friday. Westin. Contact: U/W.

May 17—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 18—**Microcomputers in Rehab Medicine.** Seattle. Saturday. Contact: U/W.

May 21—**Ballard Hospital Lectures.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 22-24—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

May 1—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

May 30-31—**Mental Health Policy Forum.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

May 31—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 6-7—**Behavioral Medicine.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

June 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Ballard Hospital Lectures.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 19-20—**Financial Planning for Physicians.** Victoria, BC. Wednesday-Friday. Empress Hotel. Contact: U/W.

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THE WESTERN JOURNAL OF MEDICINE
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In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

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Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

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Tables

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

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Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

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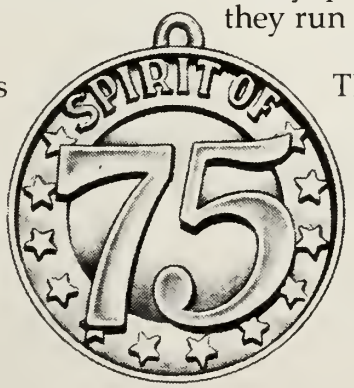

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California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and County, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: 1985—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1985—date and place to be announced.

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New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

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Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1985—date and place to be announced.

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Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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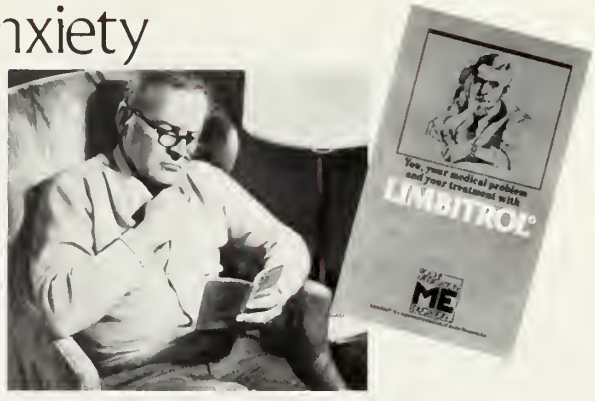
*Feighner JP: *Psychopharmacology* 61 217-225, Mar 22, 1979.



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Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use. When initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated start to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Any depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25: initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt); bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

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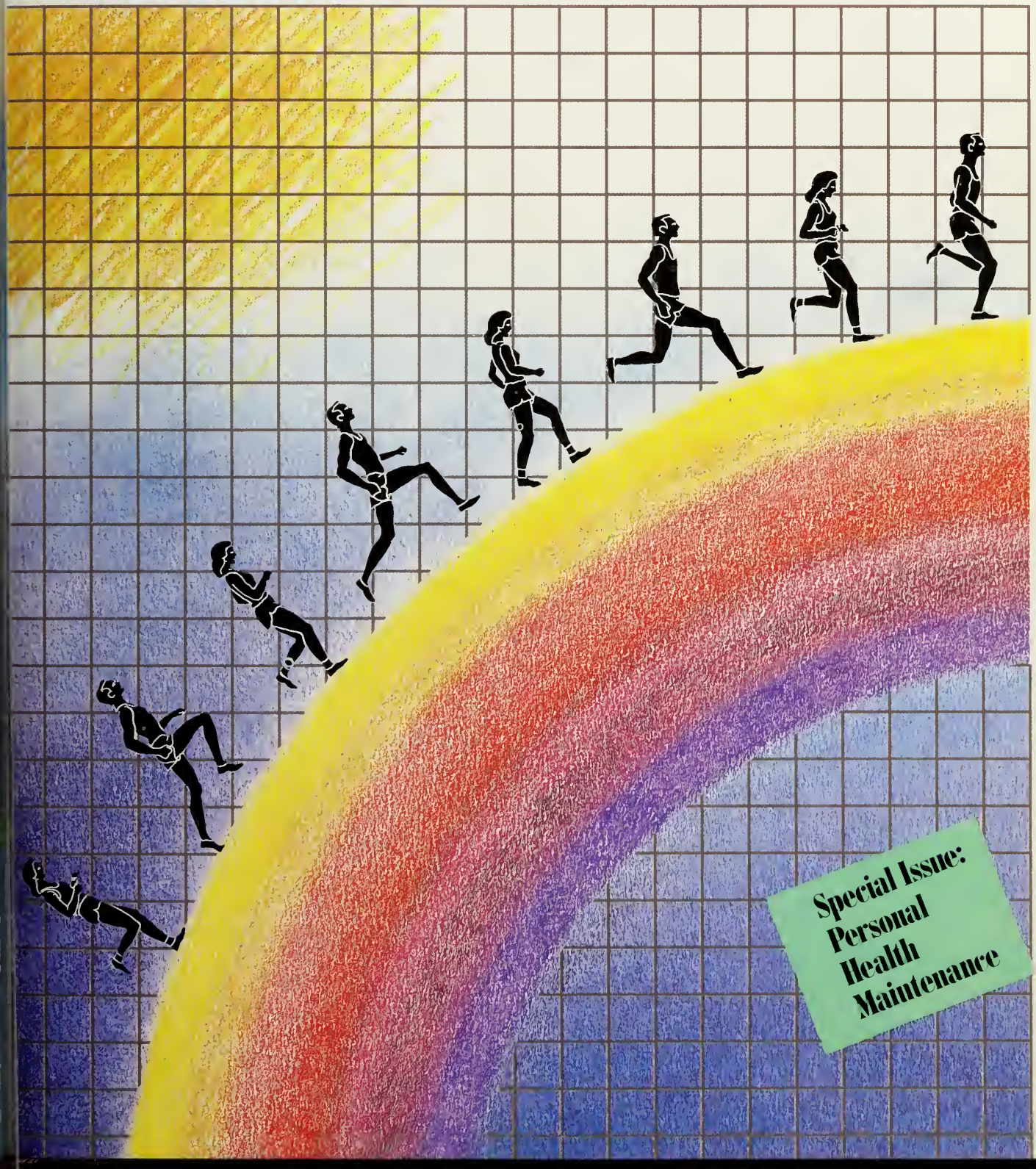

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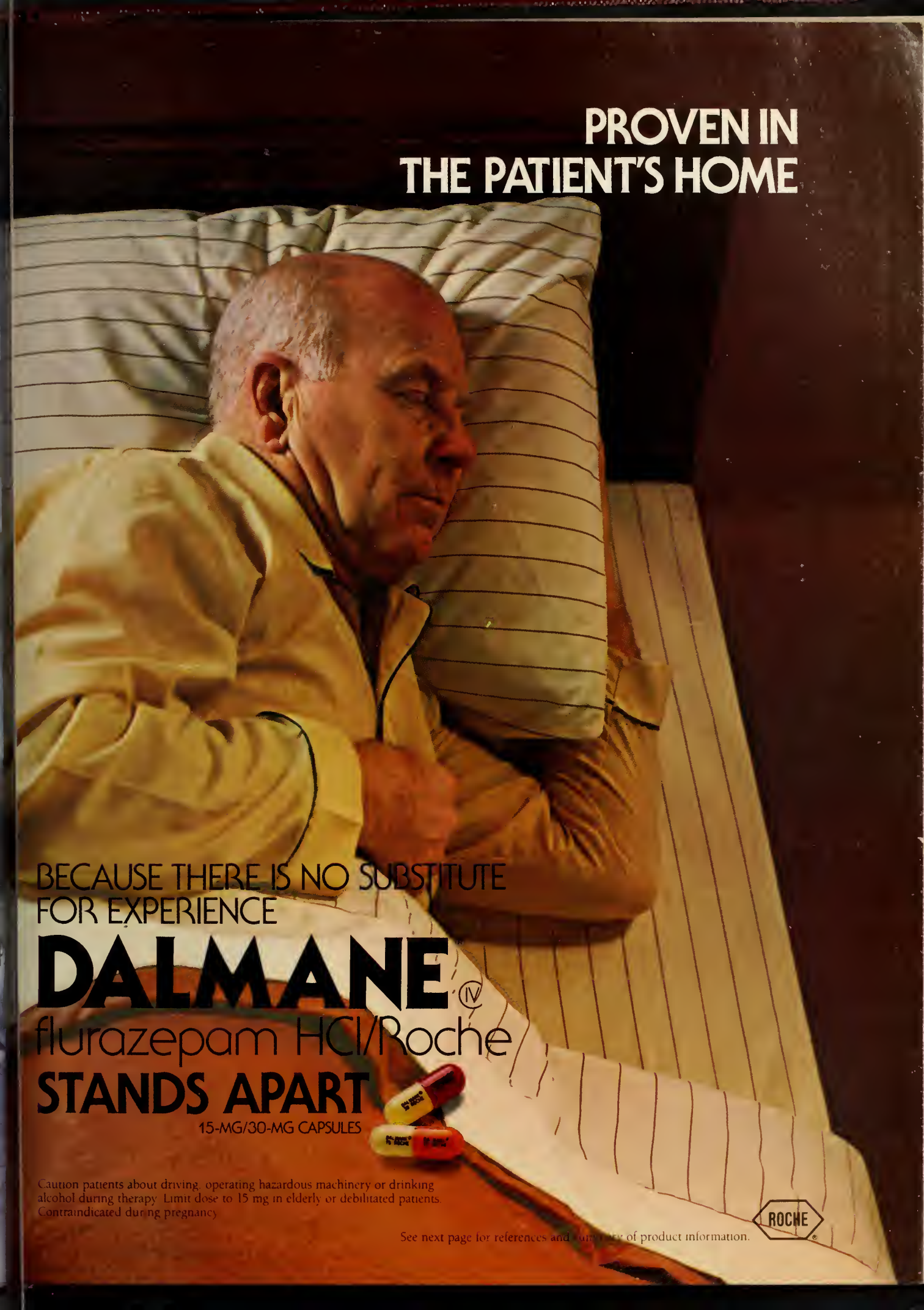
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References: 1. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM. *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983. **10.** Monti JM. *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep 5*(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

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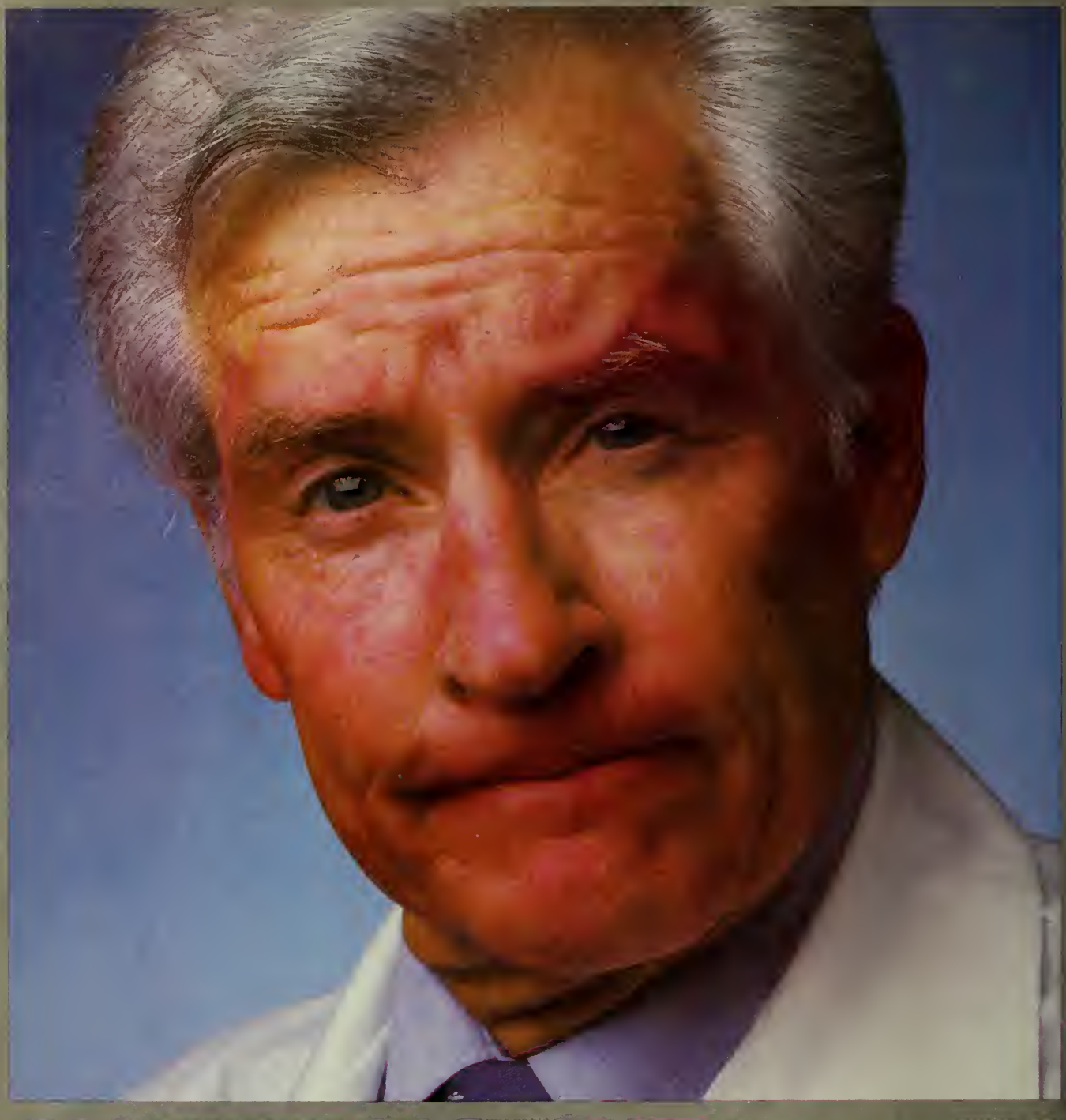

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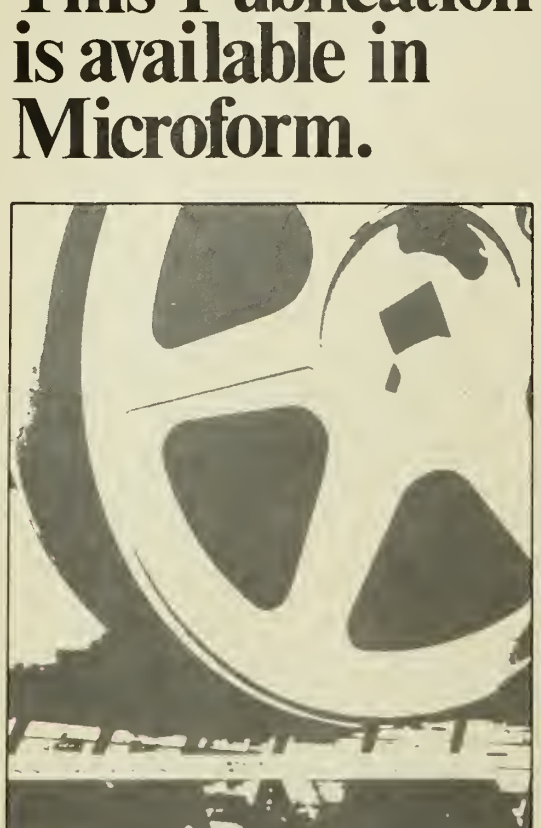

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Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

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Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function*, Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on adjacent page)

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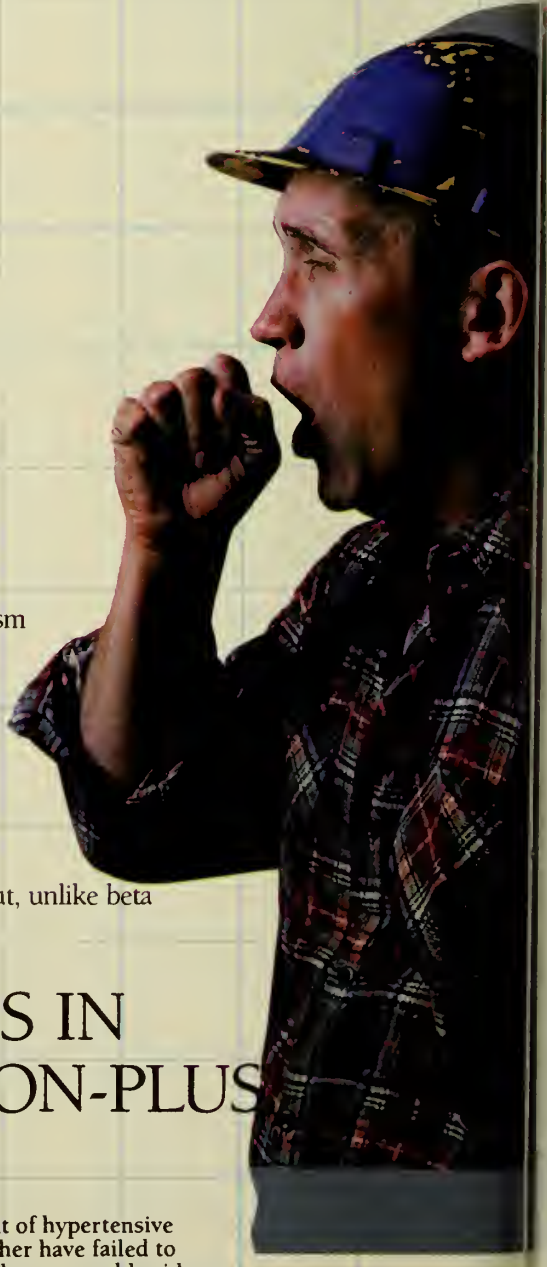

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Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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January 3-5—**Allergy and Dermatology.** Symposium Maui, Hawaii Medical Association, and Hawaii American Academy of Family Practice at Royal Lahaina Resort, Maui. Thursday-Saturday. 13.5 hrs. $275. Contact: Symposium Maui, Joe Harrison, MD, Director, PO Box 10185, Lahaina, Maui 96761.

January 10-12—**Allergy and Immune Diseases in Children.** Symposium Maui, Hawaii Medical Association and Hawaii American Academy of Family Practice at Royal Lahaina Resort, Maui. Thursday-Saturday. 13.5 hrs. $275. Contact: Symposium Maui, Joe Harrison, MD, Director, PO Box 10185, Lahaina, Maui 96761.

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January 10-13—**Anesthesia Update.** UCSD at Hotel Intercontinental, San Diego. Thursday-Sunday. 20 hrs. Fee: $100-$250. Contact: UCSD.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation and Childrens Hospital of Los Angeles at Los Angeles. Friday-Sunday. Contact: Wayne Herbert, MD, Program Dir., Ped. Anes. Fndn., PO Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

January 18-19—**Urological Cancer.** USC. Friday-Saturday.

January 19—**Avoidable Cancer: Cause and Control.** UCI. Saturday. 6 hrs. Fee: $30. Contact: UCI.

February 6—**Impact of Questionable Cancer: Treatments on Oncology Practice Today.** Hospital of Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, Coordinator of Symposium, 616 S. Witmer St., Los Angeles 90017. (213) 977-2352.

(Continued on Page 749)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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First-step blood pressure control with optimal simplicity

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Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

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Just once each day for initial therapy in hypertension.

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Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length and diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the platelets of the blood.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8950/284

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 745)

February 14-16—**Annual Oncology Review.** UCLA at Century Plaza Hotel. Thursday-Saturday. 20 hrs.

March 1-2—**Cancer and the Elderly.** West Coast Cancer Foundation at Sheraton Palace Hotel, San Francisco. Friday-Saturday. 12 hrs. Fee: $150. Contact: West Coast Cancer Foundation, 50 Francisco, San Francisco 94133.

March 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Kona Kai Club, San Diego, Sunday. 7 hrs. Fee: $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138.

CARDIOLOGY

January 12—**"Tetralogy of Fallot" Cardiac Lecture Series.** Heart Institute of the Desert at Annenberg Health Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270; (619) 568-2900.

January 18-19—**4th Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Sheraton Grande Hotel, Los Angeles. Friday-Saturday. 10 hrs. Contact: Masato Takahasi, MD, Division of Cardiology, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054-0700. (213) 669-2461.

January 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado Health Sciences Center at MGM Grand Hotel, Las Vegas. Friday-Sunday. 13 hrs. Contact: Med. Ed. Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

January 28-31—**3rd Annual Cardiology Update.** Institute for Medical Studies at Sheraton-Waikiki, Hawaii. Monday-Thursday. 15 hrs. Fee: $395. Contact: Kim Stroich, Institute for Medical Studies, 30131 Town Center Rd., Ste. 215, Laguna Miguel, CA 92677. (714) 495-4499.

February 8-10—**"Case Studies in Cardiology": A Cardiology Review for Clinicians.** The Presbyterian Heart Institute at Presbyterian Hospital, Albuquerque, NM. Friday-Sunday. 19 hrs. Fee: $150. Contact: Gilbert Raff, MD, (505) 242-2796.

February 9—**"Ischemic Mitral Regurgitation" Cardiac Lecture Series.** Heart Institute of the Desert at Annenberg Health Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270. (619) 568-2900.

February 15-17—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center at International Hotel, Palm Springs. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

February 22-24—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Americana Canyon, Palm Springs. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

March 1-3—**ECG Interpretation and Arrhythmia Management.** International Medical Corp. at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

March 13—**Cardiology: Arrhythmias-Recognition and Treatment** at LLU. Wednesday. 4 hrs.

March 16—**Cardiac Lecture Series: "Cardiovascular Trauma Texas Style."** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

March 22-24—**Cardiology for the Primary Care Physician.** UCSD at Palm Springs Spa Hotel. Friday-Sunday. 18 hrs.

March 25-29—**Vascular and Pulmonary Diseases: Diagnosis & Management.** Medical Education Resources at Sheraton Maui, HI. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Resources, 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9682.

EMERGENCY MEDICINE

January 14-18—**Postgraduate Institute for Emergency Physicians: Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 13-36 hrs. Fee: $200-$675. Contact: UCSD.

January 19-26—**Management of Traumatic Emergencies.** UCSD at Kona Surf Resort, Kona, HI. Sunday-Sunday. 21 hrs. Fee: $315-$430. Contact: UCSD.

January 28-30—**Trauma: 1985.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 20 hrs.

February 4-8—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Monday-Friday. 35 hrs. Fee: $425.

(Continued on Page 764)

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BALANCED CALCIUM CHANNEL BLOCKADE!

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

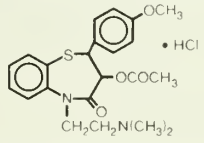
PROFESSIONAL USE INFORMATION

cardizem® (diltiazem HCl)

30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/8

Another patient benefit product from

PHARMACEUTICAL DIVISION
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ALBERT OBERMAN, MD, MPH

From the Division of General and Preventive Medicine, Department of Medicine, University of Alabama in Birmingham School of Medicine.

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ANTONIO M. GOTTO, Jr, MD; LYNNE W. SCOTT, MA, RD, and JOHN P. FOREYT, PhD

From the Department of Medicine, Baylor College of Medicine, Houston.

878 **Smoking and Health**

JESSE L. STEINFELD, MD

Dr Steinfeld is President of the Medical College of Georgia, Augusta. He served as Surgeon General of the United States from 1969 to 1973.

884 **Alcohol and Drug Use—Is There a 'Safe' Amount?**

CHARLES E. BECKER, MD

From the Department of Medicine, University of California, San Francisco, and the Division of Occupational Medicine and Toxicology, Northern California Occupational Health Center, San Francisco General Hospital Medical Center, San Francisco.

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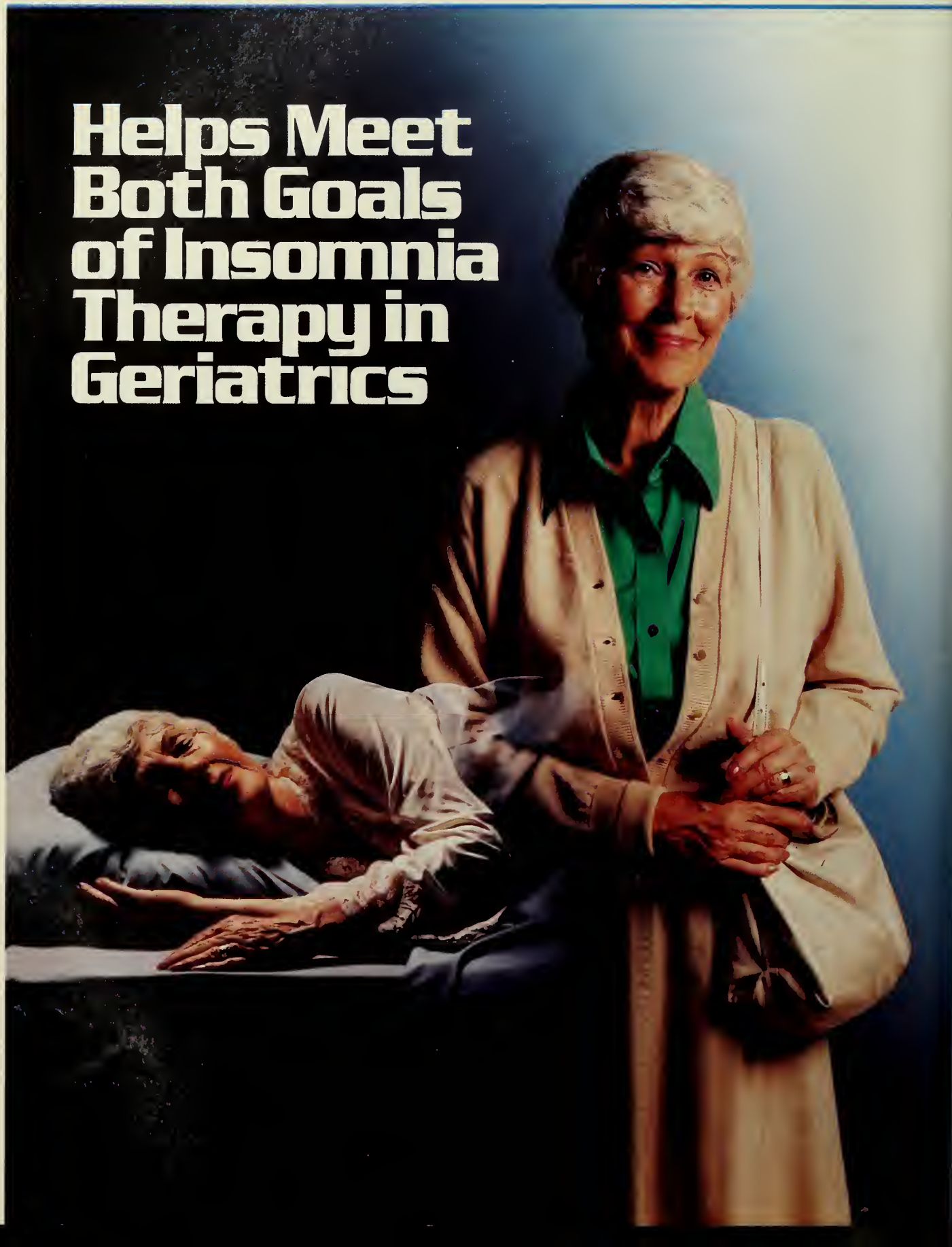
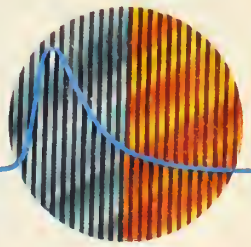
★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

Halcion® 0.25 mg Tablets

triazolam C IV



Upjohn Please see next page for brief summary of prescribing information.



Goal 1: Improved Sleep

Better Initiation and Maintenance of Sleep

- *Halcion* was found to initiate sleep in insomniac patients *within 17.4 minutes* after ingestion.
- Peak serum concentration occurs at 1.3 hours.
- Patients receiving *Halcion* were found to have 56.9% *fewer nighttime awakenings* (compared with baseline).
- Patients receiving *Halcion slept longer* each night of therapy (an average of 36 minutes longer) in comparison with baseline.

Goal 2: Daytime Alertness

Better Morning and Daytime Alertness

- *Halcion* has the shortest half-life of any benzodiazepine-derived sleep medication.
- In controlled studies, *Halcion* treated patients demonstrated *significantly better* morning and daytime alertness than flurazepam-treated patients.[1]
- Within 24 hours following a single oral dose, *Halcion* was *no longer detectable* in the plasma.
- Patients receiving *Halcion* should be cautioned about the possible combined effects with alcohol and other CNS depressants.

RAPIDLY ABSORBED FOR IMPROVED SLEEP

PROMPTLY EXCRETED FOR DAYTIME ALERTNESS

Halcion
triazolam (IV)

0.25 mg Tablets
Initiate at 0.125 mg

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Halcion Tablets
triazolam (IV)

Special Dosage Guidelines for Geriatric Patients

0.125 MG TO 0.25 MG
Initiate at 0.125 mg (half of a 0.25 mg scored tablet) until individual response is determined.

Because geriatric and/or debilitated patients respond favorably to lower doses of *Halcion*, initiation at the above dosage is recommended.

DOSAGE FOR NON-GERIATRIC PATIENTS: 0.25 MG TO 0.5 MG

Patients should be advised against engaging in hazardous tasks that require mental alertness (operating machinery or driving a motor vehicle).

Reference: 1. Ogura C, et al: Residual effects of hypnotics: Triazolam, flurazepam, and nitrazepam. *Psychopharmacol* 1980; 68:61-65.

Halcion Tablets
triazolam (IV)

INDICATIONS AND USAGE
HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS
Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS
Overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS
General: In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) possible worsening of sleep after discontinuing HALCION. Laboratory Tests: Not ordinarily required in otherwise healthy patients. Drug Interactions: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported. Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. Pregnancy: Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. Nursing Mothers: Administration to nursing mothers is not recommended. Pediatric Use: Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS
During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g. drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE
Controlled Substance: HALCION Tablets are a Controlled Substance in Schedule IV. Abuse and Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE
Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

J-3671R October 19

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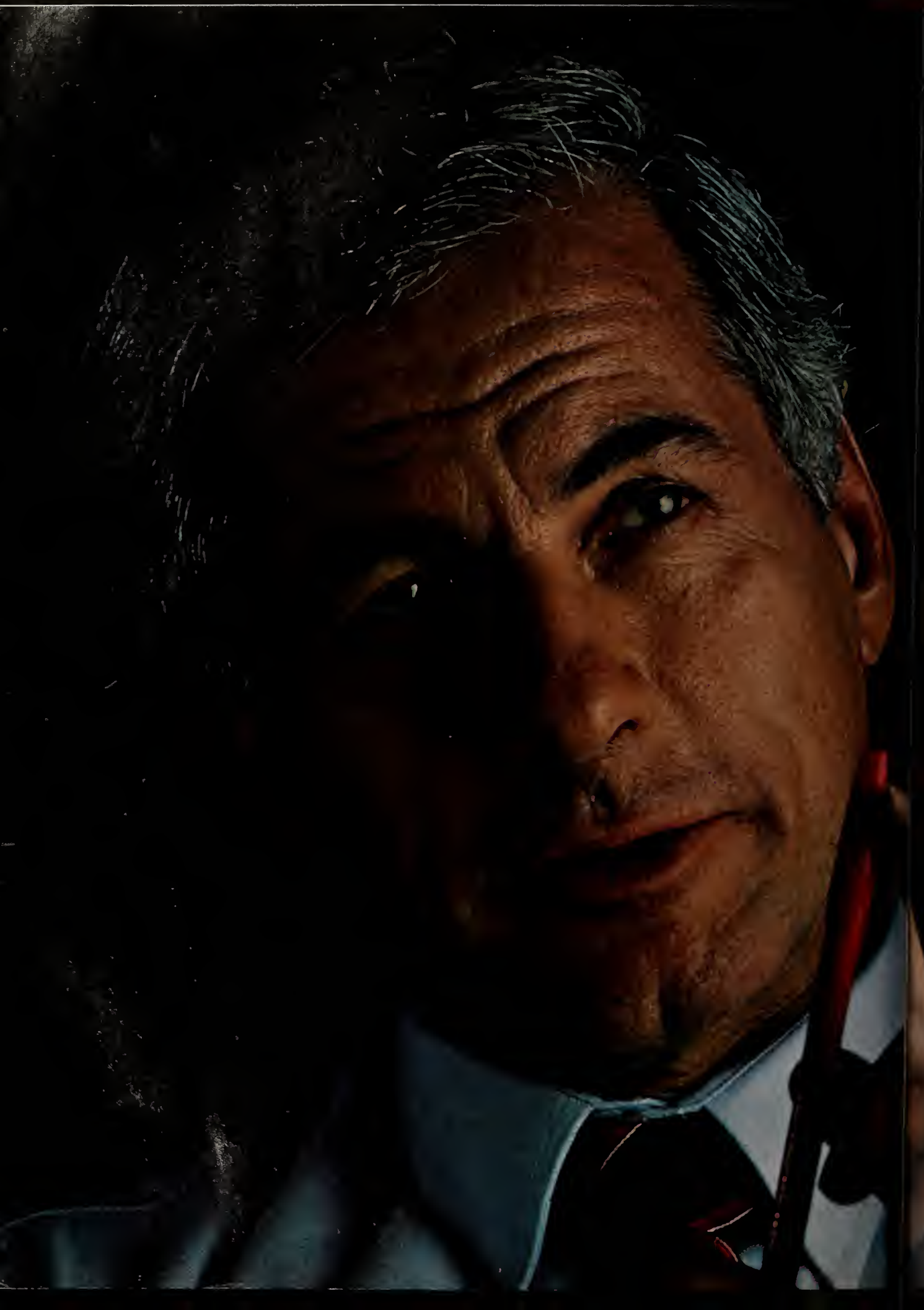

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Most doctors are pleasantly surprised to learn that the average cost of daily therapy with the world's most widely used beta blocker is so little, not much more than the cost of a daily newspaper.

When it's INDERAL tablets (propranolol hydrochloride) you want for your hypertension patients, remember to specify Dispense As Written (DAW) or Do Not Substitute on your prescriptions. That way, you can always be assured they'll get INDERAL®.

Please see next page for brief summary of prescribing information.

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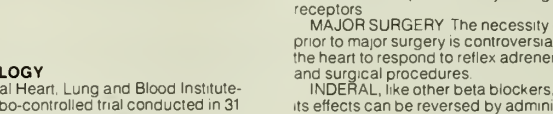
(PROPRANOLOL HCl)



10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure; certain conduction defects; angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL: In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC: Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC: A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 vs. 1,024 ng/ml·hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

•The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

9371/1184

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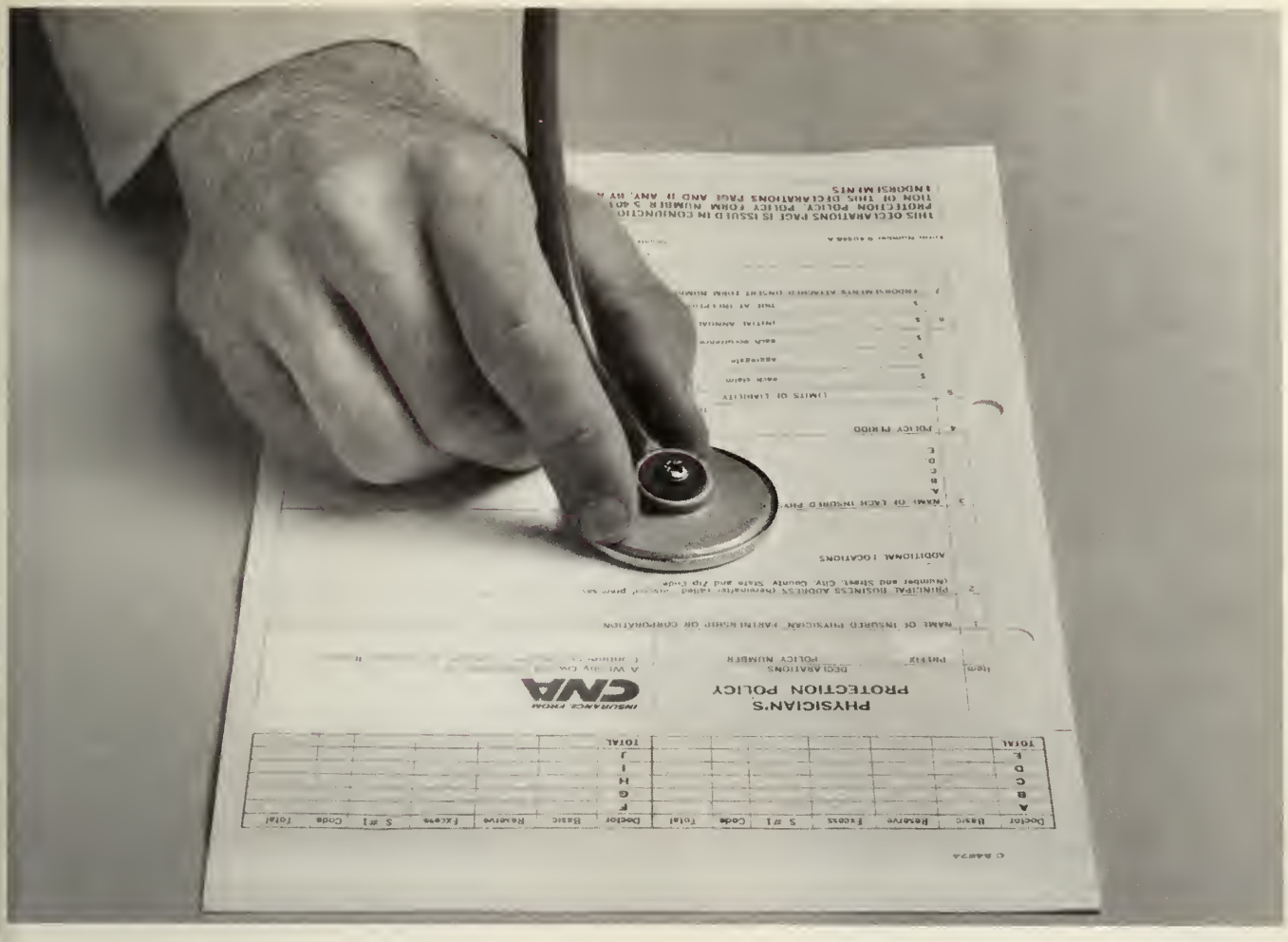

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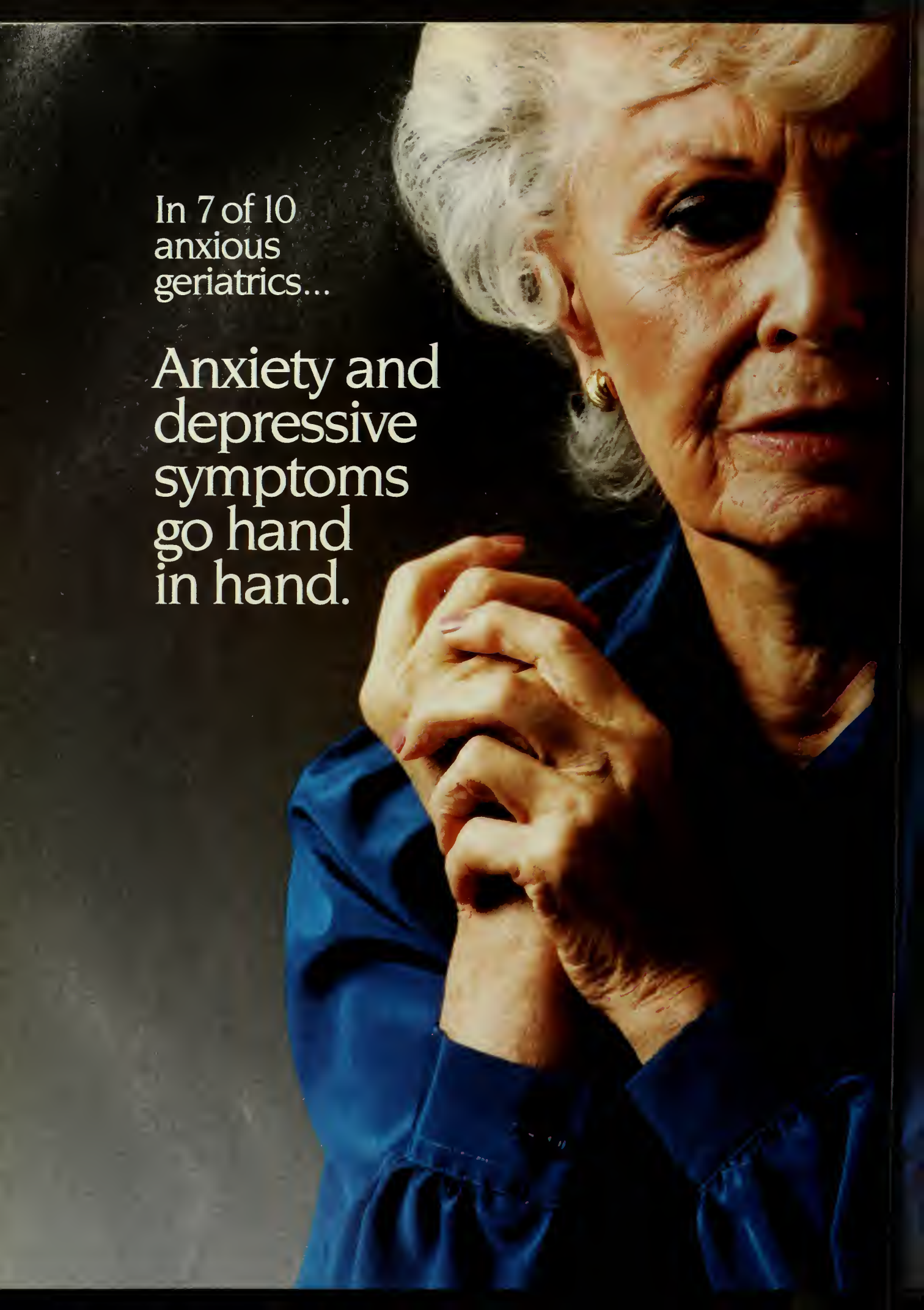
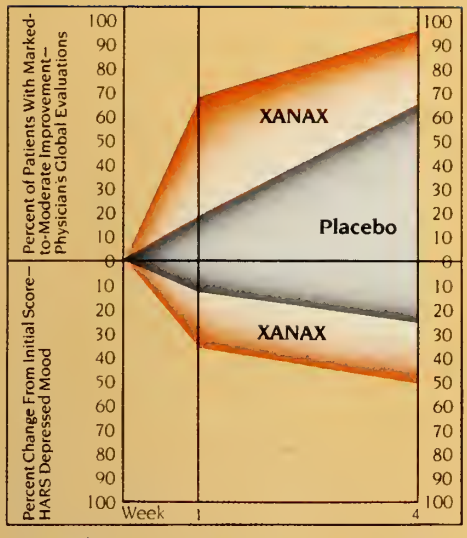
The Physicians Protection Program is available to individual physicians in Washington and Idaho and through association sponsored programs in California.

INSURANCE FROM
CNA
For All the Commitments You Make


In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax rapidly relieves anxiety with depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients *Curr Ther Res* 1984 35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam C IV

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Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℂ

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, unnalysis and blood chemistry analysis are advisable. Minor EEG changes of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg two or three times daily. Reduce dosage gradually when terminating therapy by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

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Kalamazoo, Michigan 49001 USA

CONTINUING MEDICAL EDUCATION

(Continued from Page 749)

February 24-March 1—**Emergency Medicine: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Sunday. Contact: UCD.

February 25-28—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: USC.

INTERNAL MEDICINE

January 9—**Urology—The Prostate.** LLU at LLU Medical Center. Wednesday. Contact: LLU.

January 24-26—**Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West, San Diego. Thursday-Saturday. 18 hrs. Fee: $300. Contact: UCSD.

January 24-26—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West, San Diego. Thursday-Saturday. 18 hrs. Contact: UCSD.

February 8-9—**Infectious Disease: Clinical Update.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. Contact: UCD.

February 12-17—**18th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Tuesday-Sunday. Contact: UCSF.

February 13-14—**Rheumatology Subspecialty Course.** UCSD at Town and Country Hotel, San Diego. Wednesday-Thursday. 12 hrs.

February 15-19—**10th Annual Postgraduate Topics in Internal Medicine.** UCSD at Town and Country Hotel, San Diego. Wednesday-Tuesday. 36 hrs.

February 17-22—**Advanced Problems in Infectious Diseases and Toxicology.** UCSD at Continental Inn, Aspen. Sunday-Friday. 21 hrs. Fee: $315-$430. Contact: UCSD.

February 21-24—**Federation of Societies of Neurological Science** at Hotel Intercontinental, San Diego. Thursday-Friday. 18 hrs. Contact: James Grisolia, MD, 4020 5th Ave., Ste. 404, San Diego 92138. (619) 297-1155.

February 27-March 2—**Gastroenterology Subspecialty Course.** UCSD at Town and Country Hotel, San Diego. Wednesday-Saturday. 12 hrs.

March 8-10—**Frontiers of Rheumatology.** Annenberg Center for Health Science, Rancho Mirage. Friday-Sunday. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

(Continued on Page 766)

A new low price for Motrin ibuprofen

Motrin is priced lower than Clinoril, Feldene, or Naprosyn.

The price of *Motrin* Tablets to pharmacies has been reduced as much as 35%. Patients taking the average dosage should now pay less for therapy with *Motrin* Tablets than for almost any other nonsteroidal anti-inflammatory drug you prescribe...less, for example, than for Clinoril, Feldene, or Naprosyn.

New low price means major savings.

The dramatic reduction in the price of *Motrin* Tablets means substantial savings from now on for your patients and for patients all across the country for whom *Motrin* Tablets are prescribed. And, of course, all strengths of *Motrin* Tablets continue to be available by prescription only.

Please see the following page for a brief summary of prescribing information.

Motrin® 400 & 600 mg TABLETS
ibuprofen

Good medicine...good value

© 1984 The Upjohn Company

The Upjohn Company **Upjohn** Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)
Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or nther nonsteroidal anti-inflammatory agents.
Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.
Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.
Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.
Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.
Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.
Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.
Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.
The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.
As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.
Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.
Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.
Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.
Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.
Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship
Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation, see PRECAUTIONS).
Incidence less than 1%—Probable Causal Relationship**
Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.
Incidence less than 1%—Causal Relationship Unknown**
Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.
*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)
**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.
Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.
Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.
Caution: Federal law prohibits dispensing without prescription. MED B 7-S

Motrin is a registered trademark of The Upjohn Manufacturing Company

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

CONTINUING MEDICAL EDUCATION

(Continued from Page 764)

March 13-16—**Office Endocrinology: 1985.** UCSF at Granlibakken Ski and Raquet Resort, Tahoe City. Wednesday-Saturday.

March 18-20—**Gastroenterology Course.** UCSF at Yosemite. Monday-Wednesday. Contact: UCSF.

March 19-22—**Internal Medicine Update.** UCD at Red Lion Motor Inn, Sacramento. Tuesday-Friday.

OBSTETRICS AND GYNECOLOGY

February 3-7—**OB/GYN Update: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: UCD.

February 9-10—**Los Angeles OB/GYN Forum.** Los Angeles OB/GYN Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. 10 hrs. Fee: $80. Contact: Director of Medical Education, LA OB/GYN Society, 5820 Wilshire Blvd, #500, Los Angeles, CA 90036. (213) 937-5514.

February 9-16—**13th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki, HI. One week. 20 hrs. Contact: Arlene Rogers, OSUH, Department of Anesthesiology, 410 W. 10th Ave., Columbus, OH 43210. (614) 421-8487.

February 11-15—**San Diego Abdominal and Obstetrical Imaging Symposium Update.** UCSD at Hotel Intercontinental, San Diego. Fee: $425. Contact: UCSD.

February 16-23—**Perinatal Medicine.** USC at Royal Lahaina, Maui, HI. One week.

February 23—**OB/GYN.** UCSF at Fresno. Saturday. Contact: UCSF.

March 2-9—**6th Annual Symposium on Current Topics in Obstetrics.** UCI at Aspen, Colorado. One week. 23 hrs. Contact: UCI.

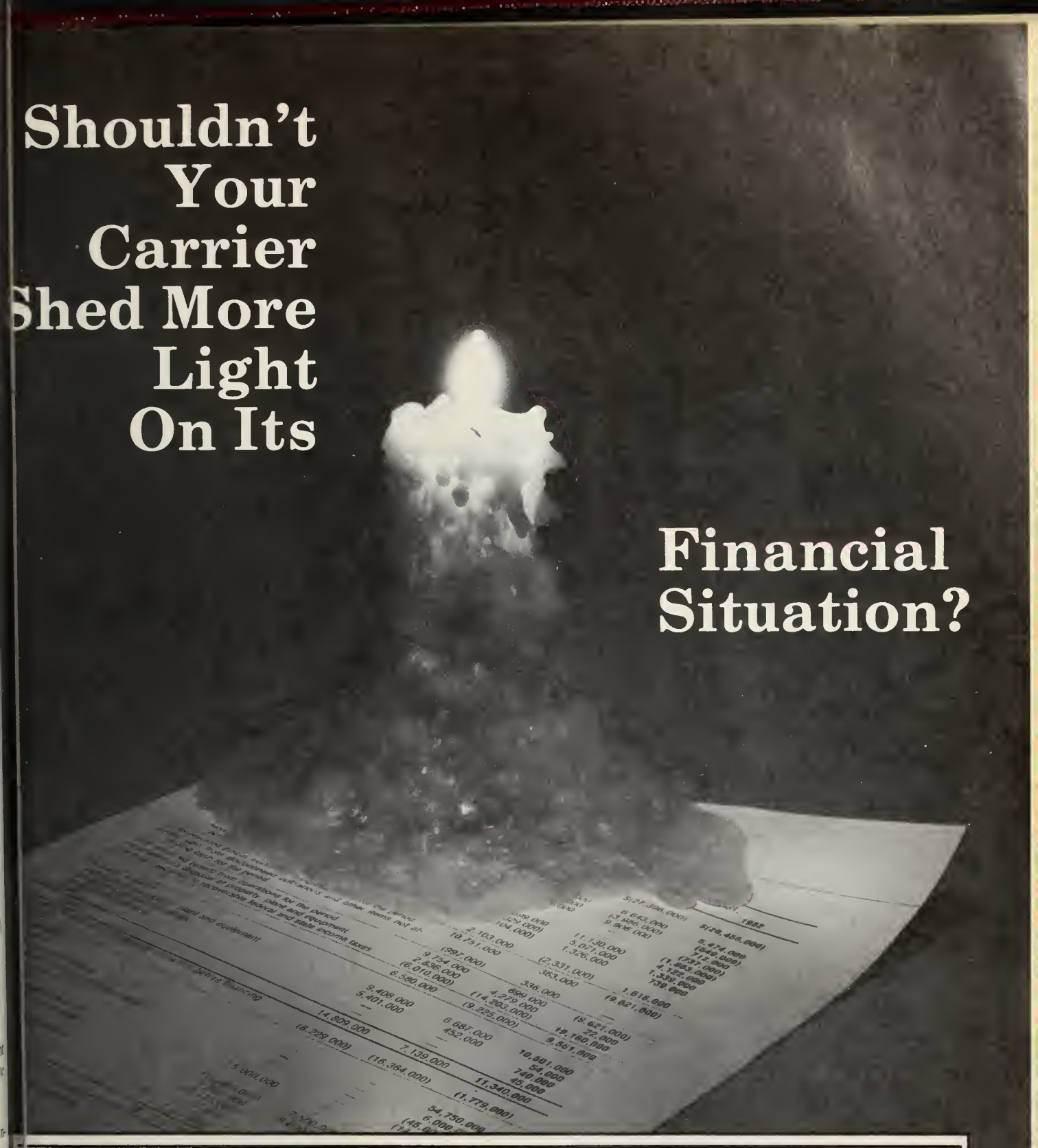
March 7-10—**Recent Advances in OB/GYN: 8th Annual.** UCSD at Hotel Intercontinental, San Diego. Thursday-Saturday. 21 hrs.

OPHTHALMOLOGY

January 24-25—**YAG Laser Source.** UCSD at UCSD Medical Center. Thursday-Friday. 12 hrs. Contact: UCSD.

(Continued on Page 909)

Shouldn't Your Carrier Shed More Light On Its Financial Situation?



Many professional liability carriers try to keep their insureds in the dark concerning their financial situation. Not Insurance Corporation of America. ICA's financial stability reflects our long-term commitment to the medical community.

Through sound management, conservative investments, and consistent reinsurance, ICA has grown to become one of the leading writers of professional liability insurance in the nation.

For further information about ICA's enlightened approach to professional liability insurance, please call 1-800-231-2615; in Texas call 1-800-392-9702. Check for availability in your state.

ICA

The Preferred Underwriter

New Hydrochlorothiazide Dosage Guidelines from High BP Joint National Committee

START WITH 25 mg.

The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends starting with the smallest effective dose in diuretic therapy. For hydrochlorothiazide the initial dosage recommended is 25 mg.

DYAZIDE® contains the dosage of hydrochlorothiazide recommended by JNC III.

DYAZIDE® also contains 50 mg. of triamterene—the initial dosage of that agent recommended by JNC III.

In Hypertension*...When you want the safety and efficacy of low dosage thiazide therapy plus potassium conservation

P R E S C R I B E

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates or narcotics). Necrotizing vasculitis, paresthesias, icterus, parotitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak unit-of-use bottles of 100.

BRS-DZ:L36

a product of
SK&F CO.
Carolina, P.R. 00630

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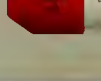
The unique red and white Dyazide® capsule: Your assurance of SK&F quality.



Special Issue:
Personal
Health
Maintenance

The Scientific Evidence for Personal Health Maintenance

During the past few years interest in health and personal health maintenance has been taking on new dimensions. At first sight one might be tempted to think that this is just another fad, here today and gone tomorrow. But this interest in health, at least in this country, is beginning to come through as something deeper, more profound, and if this is so there must be a deeper and more profound reason. Could the reason be that there are now beginning to be convincing scientific data showing that a healthy life-style and some attention to personal health maintenance can actually pay off in better health and improved well-being—and that the effort is really worth it? It would seem that this just might be the case.

There are some who may say that all this interest in wellness and fitness is purely economic. And it is true that many payors of health care are looking to wellness and fitness promotion and health maintenance to help reduce their health care costs. Many of the larger corporations in business and industry are beginning to provide exercise and fitness programs for their employees, no doubt for economic as well as social reasons.

And for some time now, and with the same motives, counseling and other services are promoted for employees who may have problems with alcohol or other drug dependence, occupational hazards in the work place or psychological maladjustment affecting their performance. But the present and obviously growing interest in wellness and fitness seems to go far beyond any interest industry, business or the payors of health care may have in "the bottom line." People are investing their own time and money in wellness and fitness activities on a scale none of us can remember ever having seen before.

One is reminded that it is only since the turn of the century that health care itself became something worth having. And its value, its use and its cost have been increasing ever since. The underlying reason for all of this, of course, is the dramatic progress that has been made in biomedical science. It now appears that progress in medical and health science has begun to show that personal health maintenance is also something worth more serious attention and that attention to it can actually pay off in better health and improved well-being for persons of almost any age. It now seems reasonably predictable that as scientific studies in this field continue to be made, wellness and fitness programs will increase in public acceptance, much as has happened with health care in recent decades—and for the same reasons.

This issue of *The Western Journal of Medicine* seeks to present the current scientific basis for many aspects of personal health maintenance. Its purpose is to provide physicians, and any others who may be interested, with authoritative information on the state of our knowledge concerning this emerging and increasingly important segment of health care.

The editors wish to thank the guest editor for this issue (who also happens to be the journal's Special Editor for Utah) for persuading authors of such distinction to write the eminently useful articles that are to be found herein, and himself for pulling it all together.

MSMW

Preface

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

The first group of papers deals with background issues. Dr Mason and Mr Tolsma outline the significance of personal health maintenance from the perspective of the federal government. Dr Breslow emphasizes the importance of patient involvement in a "health-oriented medical service." Problems that clinicians may encounter when using screening tests are discussed by Dr Friedman. Dr Collen presents an economic analysis of periodic health examinations. Sociocultural influences affecting personal health decisions are discussed by Dr Ulmer. Dr Williams stresses the importance of the family history in identifying persons predisposed to selected major diseases.

The second group of papers details specific recommendations on personal health maintenance for pregnant women, children, adults and the geriatric population. Drs Clever and Arsham provide advice on how physicians should maintain their own health.

The third group of papers focuses on health promotion. Dr Brunton discusses the role of physicians in teaching and assisting patients to change unhealthy life-styles. Dr Greenblatt summarizes the factors that contribute to good mental health. Life-style issues are presented in the papers on exercise, diet, smoking, alcohol and drug use.

The contributors hope this special issue will be useful. They also express their appreciation for the editorial assistance of M. S. M. Watts, MD; L. H. Smith, Jr, MD, and the staff of *The Western Journal of Medicine*.

JOHN H. HOLBROOK, MD
Special Issue Editor

Personal Health Promotion

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Mortality data on the leading causes of death conceal the relationship to underlying risk factors; if we classified deaths according to risk factors, annually there might be an estimated 350,000 smoking-related deaths, 200,000 alcohol-related deaths and 135,000 nutrition-related cancer deaths. Similarly, five causes of death—heart disease, lung cancer, cirrhosis of the liver, suicide and motor vehicle accidents—contribute most to the risk of dying in the next ten years for a 40-year-old white man. Review of protective factors shows that adopting and maintaining a healthful life-style can contribute to reducing risk. Practicing physicians can assume both direct and indirect roles in promoting personal health maintenance.

(Mason JO, Tolsma DD: Personal health promotion, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:772-776)

The late John H. Knowles, writing in a 1977 issue of *Daedalus*, passionately argued the case for "The responsibility of the Individual" in advancing the nation's health status:

> Central to [our] culture is faith in progress through science, technology, and industrial growth; increasingly peripheral to it is the idea, vis-à-vis health, that over 99 percent of us are born healthy and are made sick as a result of personal misbehavior and environmental conditions. The solution to the problems of ill health in modern American society involves individual responsibility, in the first instance, and social responsibility through public legislation and private voluntary efforts, in the second instance.[1]

Knowles was neither the first nor the last to observe how much individual persons can do to reduce premature death by taking responsibility for their own health. However, because Knowles was the head of Massachusetts General Hospital at that time, his detailed review of the hazards of life-style choices helped crystallize the growing realization of the limits of medical care and the promise of promoting personal health.

Personal health promotion should not be viewed simply as a question of wise or unwise choices by individuals acting alone. The idea that persons can influence their health destiny is a positive one; it is not a negative assignment of blame. However, a natural outgrowth of a concept of individual responsibility, from a public health perspective, is community responsibility—collective citizen involvement in defining priority health promotion needs and stimulating community efforts to address them. Persons can hardly be expected to avoid the health risks imposed by personal choices about life-style when they do not know or understand these risks, when they lack the knowledge or skills needed to choose a healthier life-style or, worst of all, when they seek guidance or support from their community and it is unavailable to them. Social, economic and political actions to create a community environment conducive to health are inseparable from individual responsibility for health. Personal health promotion includes all these components.

In the past decade health promotion and disease prevention have become firmly established, in principle, as central elements of the health policy of Western nations. The Canadian "Lalonde Report," issued in 1974, was instrumental in formulating the health field concept—that is, the allocation of preventable death and morbidity to four broad sources, or "fields."[2]

One field, human biology, consists of those health problems inherent in the makeup of a person and not generally considered preventable. A second, environment, consists of health problems caused by environmental and occupational exposures. A third field, health systems, deals with those health problems that can be avoided or cured by removing inadequacies in health care. The fourth field, life-style, consists of problems that arise as a result of personal behavior choices and that can be prevented by adopting or maintaining protective behaviors.

The Lalonde report was soon joined by similar national policy documents in the United States,[3,4] Australia[5] and the United Kingdom[6] (see Table 1). Two Public Health Service publications, *Healthy People: A Report of the Surgeon General on Health Promotion and Disease Prevention* and its influential companion document, *Promoting Health/ Preventing Disease: Objectives for the Nation*, both widely

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TABLE 1.—*Official Health Policy Statements That Advocate Personal Health Promotion*

Title	*Country*	*Year*
A New Perspective on the Health of Canadians	Canada	1974
Prevention and Health: Everybody's Business	United Kingdom	1976
Disease Prevention and Health Promotion: Federal Programs and Prospects	USA	1978
Model Standards for Community Preventive Health Services	USA	1979
Healthy People: A Report of the Surgeon General on Health Promotion and Disease	USA	1979
Promoting Health: Prospects for Better Health Throughout Australia	Australia	1979
Promoting Health/Preventing Disease: Objectives for the Nation	USA	1980

ABBREVIATIONS USED IN TEXT
CDC = Centers for Disease Control
HRA = health risk appraisal
WHO = World Health Organization

distributed, were viewed by the public health community as major statements of a new emphasis in US health policy. These policy documents are significant in several respects:

- They reflect their prevention priorities based directly on epidemiologic review of preventable illness and death.
- They state goals and objectives for prevention in terms of measurable disease outcomes and quantified reductions in risk.
- They identify health promotion—both in the titles and in the expected contribution to better health in the ensuing decade—as an equal partner with the more traditional public health strategies of disease prevention. In *Promoting Health/Preventing Disease: Objectives for the Nation,* 226 measurable objectives are listed as attainable by 1990; 78 of these are explicitly listed under the heading "Health Promotion." However, an additional 30 objectives, although listed under the headings "Health Protection" and "Preventive Health Services," actually address health behaviors and educational outcomes. Hence, virtually half of all the 1990 prevention targets relate to individual health promotion.

This major emphasis on individual health promotion has emerged as a result of many converging influences. First, at all levels of government, public officials are greatly concerned over the enormous increases in public expenditures for medical care. While it would be a great mistake to suppose that health promotion alone can or will stop the rise in medical care costs by 1990, attaining the national prevention objectives could postpone some of the need for services.

Second, health promotion affirms a widely held American belief in individual and family responsibility. Many Americans want to control their own lives and make their own life-style decisions. They welcome programs that help them adopt or maintain healthful life-styles. Opinion polls have documented substantial public recognition of the value of promoting health and of public support for programs.[7]

A third basis for this new emphasis is the body of knowledge that has resulted from the past three decades of epidemiologic research. It is unlikely that an entire issue of a major medical journal could be devoted to the topic of health promotion had it not been for the brilliant work of epidemiologists, biostatisticians and clinicians during this period. Numerous studies and trials have established significant associations and causal relationships between a variety of behavioral risk factors and the major health problems of today, and have documented that improved outcomes result from reductions in risk factors. In a very real sense, health promotion is "applied epidemiology."

Thus it is not surprising that a high priority on promoting health is evident in policy documents based on epidemiologic reviews of health-status data. This can be shown with two analyses of vital statistics data.

Life-style-Related Mortality

In the United States, about 1.9 million people die each year. The leading causes of death—heart disease, cancer, stroke, accidental injury and pneumonia/influenza—are well known. Many of these deaths are premature, but their relationship to preventable risk factors is obscured by our disease-organ system schema for classifying vital events. Consider how the vital statistics data might look if we classify deaths according to risk factors.

Smoking-Related Deaths

Cigarette smoking is the single most preventable health problem in America today. In 1965, the year after the first Surgeon General's report on smoking, the prevalence of smoking among adults was 42%, and it declined steadily over the next two decades.[8] However, this trend masks a substantial increase in smoking among women during the same period. In cooperation with states, the Centers for Disease Control (CDC) conduct surveillance of behaviors of public health significance, including smoking. The CDC's behavioral risk factor surveillance data indicate that 31.5% of American men and women still smoke (Table 2).

Cigarette smoking accounts for an estimated 350,000 deaths each year.[9] However, these deaths are tabulated under heart attacks, cancer and chronic obstructive lung disease. The shocking dangers to which 50 million smokers are exposed are not obvious to them or to their families and friends. To highlight the dimension of the problem another way, imagine the public outcry if 1,000 people died as a result of a natural disaster. Yet, 1,000 people die *every day* from cigarette smoking, and it goes unrecorded and unremarked.

Alcohol-Related Deaths

While a significant fraction of American adults who use alcoholic beverages do so moderately, the misuse of alcohol is still an important cause of premature death. Behavioral risk factor surveillance data suggest that 22.7% of adults have had five or more drinks on an occasion, one or more times in the past month (Table 2). Moreover, 6.2% reported driving after having too much to drink one or more times in the past month. (These data become even more startling when age- and sex-

TABLE 2.—*National Prevalence Estimates for Adults, by Sex, Behavioral Risk Factor Surveys, 1981 Through 1983*

Risk Factor	*Men*	*Women*	*Total*
Cigarette smoking*			
Prevalence (%)	34.0	29.1	31.5
95% CI	(32.0, 35.9)	(27.5, 30.8)	(30.2, 32.7)
Heavy drinking†			
Prevalence (%)	33.4	12.9	22.7
95% CI	(31.4, 35.4)	(11.7, 14.7)	(21.5, 23.9)
Obesity‡			
Prevalence (%)	23.6	21.7	22.6
95% CI	(21.8, 25.5)	(20.3, 23.2)	(21.5, 23.8)

CI = confidence interval

*Current smoker.

† Defined as a person who has drunk five or more drinks on an occasion, one or more times in past month.

‡ 120% of ideal weight (defined as the mid-value for a medium-frame person on the 1959 Metropolitan Life Insurance Company height/weight tables).

From the Centers for Disease Control Behavioral Risk Factor Surveillance System (combined state surveys covering residents of all states except Hawaii).

specific prevalences are calculated. One of every *seven* young men reported drinking and driving in the past month.[10]) Alcohol abuse accounts for an estimated 200,000 deaths annually,[11] but, again, these are tabulated as deaths due to motor vehicle and other accidents, cirrhosis, homicide and suicide, and head and neck cancers.

Nutrition

Diet and nutrition are clearly significant to health, although the direct contribution that a prudent diet makes to health promotion is hard to measure. Even after controlling for other risk factors, obesity appears to be associated with an increased cardiovascular risk.[12] In addition, behavioral risk factor survey data indicate that 22.6% of adults are overweight—that is, 120% or more of "ideal" weight for a reference population (see Table 2). Recent results from clinical trials conducted by the National Institutes of Health suggest that dietary change can reduce high cholesterol levels and that this has a protective effect on cardiovascular outcomes.[13] The evidence that various common types of cancers are avoidable by dietary means is plausible but controversial. Doll and Peto estimate that it may ultimately be possible to reduce US cancer death rates by as much as 35% through practical dietary means.[14] If that is so, some 145,000 cancer deaths per year could be classified as nutrition-related.

When mortality data are recast in this fashion, the importance of individual health promotion is inescapable.

Probability of Dying in the Next Ten Years

The Centers for Disease Control have been actively involved in developing a health promotion tool known as the health risk appraisal, or HRA. HRA is a computer-based inventory that allows a person to estimate his or her risk of dying in the next ten years based on a profile of that person's health behavior—smoking or not, using seat belts or not, controlling high blood pressure or not, and so forth. As the base for these computations, HRA uses age-, race- and sex-specific tables on the probability of dying in the next ten years, by specific cause. The HRA uses epidemiologic relative risks associated with reported health behaviors to calculate increments and decrements in the probability of dying. The method was originally developed to help physicians practice "prospective medicine."[15]

Today health risk appraisal is conducted in a variety of settings. It is used to help people understand changes in health behavior that can make the greatest impact on their life expectancy, and to motivate them to become involved in the health promotion programs offered by HRA sponsors.

The same data set can be used qualitatively to compare two strategies: one is the contributions that more and better medical care can make to reducing risk of premature death, the other the contributions that protective behaviors can make. That is, among 40-year-old white men, there would be an estimated 4,578 deaths in the next ten years per 100,000 population.[16] Five causes of death, however, account for half of the deaths among white men in this age group.

The leading cause of death is heart disease (Table 3 highlights some of the major protective factors against heart disease). The US death rate from heart disease has been dropping quite dramatically for 16 years. No one knows the specific contribution of each factor, but it is reasonable to attribute this improvement to a number of changes:

- Over the past 20 years at least a portion of the American public has made striking behavioral changes: some have been *dietary*—switching from saturated fats to unsaturated fats.[17] Some have involved *exercise.* Millions of Americans have incorporated exercise as part of leisure-time activities, the cardiovascular benefits of which may be substantial.[18] Most significant of all, during the 15 years after the first Surgeon General's report on smoking, an estimated 30 million adults stopped *smoking.*[19]
- There have been important advances in cardiology, coronary bypass procedures, hospital coronary care units and emergency services.
- Controlled trials show that even modestly increased blood pressure increases the risk of cardiovascular disease. This knowledge has been accompanied by significant improvements in controlling blood pressure—partly through medical strategies (drug therapy) and partly through behavioral strategies (weight control and exercise).
- Recent research has confirmed that lowering the cholesterol level reduces the risk of coronary heart disease—again,

TABLE 3.—*The Five Leading Causes of Dying in the Next Ten Years for 40-Year-Old White Men and Protective Factors*

Leading Cause	*Major Protective Factors*
Heart disease	Coronary care and EMS—medical advances
	High blood pressure—control
	Cholesterol—reduced
	Diet—lower saturated fat
	Exercise—increased
	Smoking—reduced prevalence
Lung cancer	Nonsmoking
	Protection from occupational or environmental exposure
Cirrhosis of the liver	Alcohol—moderate use
Suicide	Hope, meaning in life, family and community support, treatment of depression, nonuse of drugs/alcohol
Motor vehicle accidents	Alcohol—not drinking and driving
	Seat belts—regular use
	Roadways, vehicles—safer design
	Trauma care and EMS—medical advances

EMS=emergency medical services

From the Center for Health Promotion and Education, Centers for Disease Control, 1982.[16]

partly through medical treatment (drugs) and partly through behavioral means (diet, exercise).[13]

Thus, for the 40-year-old white men cited in our example, it is reasonable to conclude that the risk of dying of heart disease in the next ten years is substantially related to their health behavior choices.

This is even more obvious when we consider the probability, for 40-year-old white men, of dying in the next ten years from the second most frequent cause of death, lung cancer. The 1982 Surgeon General's report on the health consequences of smoking stated that an estimated 25% of all cancer deaths in the United States are due to lung cancer and 85% of these are due to cigarette smoking.[20] Refraining from smoking is the primary intervention, with medical care having modest impact on survival once lung cancer develops (Table 3).

For 40-year-old white men, the next three leading causes of death in the next ten years are cirrhosis of the liver, suicide and motor vehicle accidents (Table 3). Known or potential risk-reducing opportunities exist in each of these categories.

Obviously, the point is not that medicine is unimportant—the life tables already incorporate the life-saving contributions of past medical care advances. Rather, the findings show how heavily the risk of dying in the next ten years is weighted by life-style-related ailments, and thus how much healthful behavior choices could contribute to reducing risk.

The Role of Health Education

At the 1983 General Assembly of the World Health Organization (WHO), Margaret Heckler, Secretary of the US Department of Health and Human Services, described the central role health education must play in addressing the health problems of the future:

> In the United States, we have placed new emphasis on the prevention of disease. Of special importance is the development of a national awareness that individuals must take action on their own behalf to prevent disease and to promote good health. This new emphasis recognizes a simple fact: that even though our medical resources can go far in curing disease, each individual can make daily choices to prevent disease. WHO's goal of health for all by the year 2000 embodies the same principle and depends on the development of a global awareness of the individual's responsibility for his or her health.
>
> We have learned much about the relationships between health and individual action, but the real challenge is to convey this information and motivate individuals to act.

Health education is frequently perceived as lacking evidence of efficacy, which sometimes is translated, inaccurately, to mean "ineffective." The lack of documentation is quietly changing. Rigorous evaluation models have been described.[21] Moreover, in recent years, excellent studies have emerged in the public health literature. In one, Morisky and colleagues report substantial reductions in hypertension-related mortality among low-income black women participating in a health education program in a hospital setting, compared with a control group not in the program.[22] Warner and Murt's cohort analysis indicates that more than 200,000 premature deaths were averted as a result of antismoking campaigns between 1964 and 1978.[23] Recently, Sexton and Hebel reported on a clinical trial conducted among pregnant smokers in a control group and in an experimental group that received smoking cessation services. The trial documented reductions in maternal smoking and increases in infant length and birth weight.[24] It is increasingly clear that well-conceived, well-designed and well-conducted health education programs can yield measurable outcomes.

Community-Based Health Promotion

The focus of health promotion activities at the Centers for Disease Control is increasingly on collaborating with states to stimulate effective community health promotion efforts. The 1990 prevention objectives are given in terms of national outcome measures, but national outcomes are nothing more than a summation of community outcomes. One essential requirement for a community-based approach is acquiring and using community-specific data. We recommend the use of risk-factor prevalence surveys, vital statistics and demographic information to characterize target groups.

A community-based approach also requires convening a representative cross-section of health professionals and community leaders to reach consensus on the priority health problems in the area toward which health promoting activities may be directed. Some of these may be educational, to support individual behavior change—such as smoking prevention programs. Others may be communitywide, to promote recognition of healthful life-styles as a community norm—such as the passage of measures requiring the use of child safety seats in automobiles.

All of a community's institutions need to be mobilized for this effort. Schools need to offer effective school health education programs; despite the availability of high-quality curricula, only a small fraction of the nation's schoolchildren are exposed to them. The worksite offers an attractive setting for promoting health when business or labor unions, or both, choose to sponsor activities for workers. State and local health departments and community voluntary agencies are playing an increasing role in sponsoring programs. Health care facilities have been active in patient education and can be an excellent focus for personal health promotion programs as well. For example, some health maintenance organizations and community hospitals have begun to offer programs for

patients and staff and, in some cases, for the community at large.

Physicians' Role in Promoting Health

If the medical care sector is in fact a logical setting for health promotion and education, it is difficult to escape the conclusion that physicians should be active participants. Dismukes and Miller, in a commentary on the role of physicians in promoting health, note that most physicians enjoy good health and are more likely to practice good health habits than other populations. Yet, Dismukes and Miller also note that among physicians there is little interest in, and even active resistance to, the introduction of health promotion in medical encounters: "This attitude creates a strange paradox for the medical profession. Physicians have discovered some secrets of better health, but are reluctant or ineffective in communicating them to their patients."[25] It is not only a paradox but an irony, for medicine is able to contribute much more than it does. There are in fact multiple roles physicians can play in personal health promotion.

Public respect for the medical profession accords physicians a role as community leaders. Physician leadership can help galvanize a community to recognize the need for promoting healthful activities and to mobilize the human and financial resources to respond. More particularly, as public health departments move into health promotion, medical societies and practicing physicians need to encourage and support local health officials.

In addition, primary care offers a uniquely appropriate setting for integrating health promotion into health-focused service delivery. Nelson and Simmons note that three fourths of the population visit a physician annually, are likely to need preventive activities regardless of the purpose of the visit and, because of their high regard for their personal physician, are likely to grant them "great influence over health attitudes and behavior, particularly in the long run."[26]

Russell and associates evaluated a simple one- to two-minute smoking education effort directed by a group of British physicians to their smoking patients. One might view the effort as ineffective because only about 5% of the patients stopped smoking (one-year follow-up). However, Russell and co-workers point out that the net yield of ex-smokers was the equivalent of 25 successes per physician each year. To put it another way, "if all of 20,000 or more GPs in Britain were to adopt this simple measure the total could exceed half a million ex-smokers a year."[27] If the nearly 50,000 physicians who read *The Western Journal of Medicine* were as effective in this regard as the British physicians included in the study by Russell and associates, the equivalent yield would exceed 1 million ex-smokers a year. It is hard to imagine another health education measure with equivalent potential.

All practicing physicians are involved in health communication on a daily basis. The only question is the degree to which they acknowledge the role and the skill they bring to the interactions. Realizing the promise of personal health promotion in the 1980s does not require that physicians cease to be concerned with diagnosing and healing current ills, but rather that they broaden their interests to protecting the current health of patients and their families.

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Physician-Patient Partnerships for Lifelong Health Monitoring

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Progress against disease has created in some parts of the world a situation in which people can expect good health into the eighth decade of life and beyond. Ideally that involves a physician-patient partnership for health maintenance, wherein a patient actively develops a life-style that is conducive to health.

The scientific base for health maintenance has been growing through epidemiologic demonstration of the relationship between health and such living habits as smoking, diet, exercise and the use of alcohol, and the significance of blood pressure and other precursors of health effects that can be determined by physical examination.

Lifelong health monitoring of patients by physicians builds on this scientific base for health maintenance, which merely extends the presently well-established schema for monitoring health during pregnancy and infancy. Public readiness for a health-oriented, in addition to a disease-oriented, medical service is growing.

(Breslow L: Physician-patient partnerships for lifelong health monitoring, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:777-781)

During the past five or six decades people in our society increasingly have placed responsibility for their health in the hands of physicians. The obvious potential of modern medicine for dealing effectively with many diseases, including several forms of cancer and other highly malignant conditions, has inspired that confidence.

Advances in longevity and disease control have been so striking, in fact, that people and their physicians are now becoming concerned about a new health problem: how to maintain health rather than merely preserve life and struggle against disease.

Trends in Physician-Patient Partnership for Health

Throughout history the main focus of physicians in serving their patients has been to restore health that has been damaged by some pathologic condition. Recently, however, progress in overcoming and even preventing disease, for the first time in the history of humanity, has created a situation in which most persons can seek health and not just seek to overcome disease. Americans, for example, now live typically into the eighth decade of life having escaped the effects of serious disease almost all of their lives.

In these new circumstances people and their physicians are increasing their attention to achieving health in the positive sense, sometimes called "wellness," beyond disease control. Nowadays, to a substantial and growing proportion of people, health means more than simply having no condition that fits the nomenclature of disease. It means the joy of getting the most from life—incidentally, life that is extending faster after age 65 than in all the years up to that time. People understandably want to enjoy all those years to the utmost; avoiding or curing the conditions that previously devastated them is good but not enough.

Meanwhile, a second recent trend is affecting the health task and especially the role of physicians with their patients: the tendency for people to assume more responsibility for their health, including both its restoration when necessary and its maintenance throughout life.

In respect to treating disease, people are entering onto what physicians have long regarded as their own turf. For example, until quite recently radical mastectomy dominated the breast cancer therapy scene; no one, not even physicians, dared challenge the dogmatic followers of Halsted. Nowadays, however, clinicians have established a considerable array of

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therapies. In this changed circumstance and reflecting other new attitudes, a woman with the disease not uncommonly will study her own situation. She may consult friends, relatives and more than one physician, and then seek arrangements with a physician who will treat the problem according to her views. The situation occasionally seems to entail physician, not patient, "compliance." Obviously, extreme forms of that trend carry serious hazard to patient welfare; how far it will develop and how physicians will deal with it remain to be seen. Giving more complete information concerning therapeutic options and drawing patients into the decisions are, nevertheless, becoming the mode. Families also are entering the treatment decision-making process—for example, in selecting procedures for care of the dying.

Even more than in the case of treatment, steps toward health maintenance involve patient participation. Recognition that diet, exercise, the use of cigarettes and alcohol and other features of daily activity profoundly influence health is affecting the behavior of both physicians and their patients. The current decline in cigarette smoking illustrates the trend. In that regard physicians have been more prominent as exemplars than in patient counseling. Increasing attention to life-style for health in the United States opens the possibility that a genuine partnership will evolve between physicians and the public, both for maintaining health and for restoring it.

The notion that physicians as part of their work should concern themselves with what people do in their daily lives is, of course, not new. In ancient civilizations medicine was closely linked with diet and other aspects of everyday life. About 2000 BC, for example, a Chinese physician prescribed "Cereals for energy, fruits for accessory, animals for benefit, vegetables for supplement" (Xa Da-dao, "A Brief Overview of the History of Nutrition in China," unpublished document, February 10, 1981); with a broad interpretation to the word "animal," the prescription could hardly be improved today. The idea of a balanced diet was only one of many contributions by Chinese medicine to sensible nutrition. More than 1,000 years before Western medicine discovered the cause of beri-beri, Chinese physicians wrote that it could be cured by eating rice polishings. During the Sung Dynasty (900-1279 AD) a book called *Tea* or *Chia* advised drinking boiled water to prevent diseases carried by water. That was several centuries before Snow or Pasteur.

Turning to the origins of our Western tradition in medicine, the Hippocratic treatise *Ancient Medicine* noted that "the general discovery of foods to suit all conditions finally resulted in the birth of medicine. People learned by experience to do certain things and to avoid others in order to maintain health.[1] In writing about Galen, Sigerist has observed that his idea of hygiene was "a correct amount of food, drink, sleep, wakefulness, sexual activity, exercise, massage, etc."

Modern biochemistry and other medical sciences are an important aid to the wisdom of the human body, but they do not constitute that wisdom. People and their physicians have learned through the ages what activities make a healthful life-style and they generally try to follow that way of living.

Scientific Base for Health Maintenance

Life insurance actuaries in the 1930s published data showing that mortality is higher among people who are obese or who smoke cigarettes. Their companies raised premiums for those overweight in one of the first major moves to incorporate a risk factor beyond age and sex into life insurance payment structures.

Two decades later epidemiologists had proved cigarette smoking to be a cause of lung cancer and other diseases. Cardiologists in the 1970s discovered that identifying and aggressively treating persons who had only moderately elevated blood pressure yielded a better outcome than if they received little or no attention. Meanwhile, further understanding of risk factors for health and how to deal with them was rapidly emerging. This growing comprehension of the natural history of the major epidemics in our time—coronary heart disease, lung cancer and others—yielded two possibilities for intervention.

One approach was to detect and treat early stages of disease before full clinical manifestation occurred; for example, cervical carcinoma in situ. That idea can, of course, be extended to defining and seeking optimum levels of serum cholesterol and body fat, rather than just combating hypercholesterolemia and obesity. Another approach was to identify and try to influence personal habits that largely determine disease and health, such as exercise and diet.

The Framingham study disclosed that cardiovascular disease was 20 times more likely to develop in eight years in a 45-year-old man who had glucose intolerance, a systolic blood pressure of 195 mm of mercury, a serum cholesterol level of 285 mg per dl and who smoked cigarettes than in a 45-year-old man who had normal glucose tolerance, a systolic blood pressure of 105 mm of mercury, a cholesterol level of 185 mg per dl and who did not smoke cigarettes.[2] Each of these factors added independently to the risk. If one considers these criteria extreme, assume good glucose tolerance in both men, one with a systolic blood pressure of 165 mm of mercury who smokes cigarettes and with a serum cholesterol level of 235 mg per dl, and the other who does not smoke cigarettes and who has a systolic blood pressure of 135 mm of mercury and a serum cholesterol level of 185 mg per dl. With these measurements, the difference in risk is fourfold.

From a study in Alameda County, California, seven so-called health habits were identified: eating moderately, eating regularly, using alcohol moderately or not at all, not smoking cigarettes, eating breakfast, exercising at least moderately and sleeping seven to eight hours.[3] At every age, from 20 to 70 years, those who followed all seven health habits had better physical health than those who followed six, six was better than five, five better than four, four better than three and three better than two or fewer. At age 45 a man with none to three of the habits had a life expectancy of 22 more years—that is, to age 67; four to five habits, 73 years, and six to seven habits, 78 years.

Dozens of additional studies add to the scientific base for considering both physical measurements and behavior in health maintenance.

Basis in Medical Practice for Health Maintenance

While physicians generally have focused on restoring health after it is lost—that is, diagnosing and treating disease—in certain fields of medical practice health maintenance has already become a major theme.

Obstetricians have long devoted themselves primarily to guiding health during pregnancy. Regimens for the medical

care of women during pregnancy and parturition have become quite well standardized. Defining these regimens and helping women to incorporate them into their lives while bearing children have, in fact, attracted the major efforts of obstetricians for several decades. Strikingly reduced maternal mortality has accompanied, and in large part probably been attributable to, these efforts. Better care of pregnant women may also have contributed substantially to the decline in infant mortality. In pregnancy the aim has shifted toward maintaining or even improving health, not merely avoiding the potential disasters of that period of life.

In pediatrics, likewise, physicians are concerned with much more than treating illness and injury. Beyond specific immunizations to strengthen bodily resistance against several childhood diseases, the practice of pediatrics has established procedures for bolstering the health of children, such as through diet and behavioral influences. In this endeavor pediatricians have clearly entered on a partnership with mothers, and to some extent fathers and the children themselves, to provide the best possible conditions for healthy growth and development.

This approach to health care is extending beyond the prenatal, infant and childhood periods into adult life. Many practitioners of general internal medicine and family medicine find themselves increasingly occupied with periodic health appraisals and with guiding their patients based on such appraisal. This aspect of medicine also appeared years ago in the practice of large corporations that sent senior executives to leading clinics for health maintenance service.

Public Readiness for Health Maintenance

A 1978 Louis Harris poll included this item:

> There are two kinds of medicine, one curative—which treats and seeks to cure people who are sick; and another—preventive—which seeks to prevent people who are well from becoming sick. At the moment, do you think our health care system has got the balance of *curative* and *preventive* medicine about right, or should we be giving more emphasis to either one or the other than we do now?[4]

In a summary of the responses, the following was stated:

> A substantial 42% plurality of the American people believes that more emphasis should be given to preventive medicine and less to curative. Only 10% think that more emphasis should be given to curative medicine, while 33% think that our health care system has got the balance about right now.
>
> Very substantial majorities of both employers (79%) and labor union leaders (89%) think that more emphasis should now be given to preventive medicine.

While the term used is preventive medicine, the clear notion is to move from simply repairing health damage to something more positive. Further items in the Harris survey indicated substantial interest in adding health promotion programs to health plans, even if that entailed an added cost of $5 per month.

In another survey conducted in 1983 by Louis Harris and Associates, almost the same item as that cited above was used. By that time the general public's response had shifted even more strongly toward prevention.[5] Only 18% considered that the balance was right, whereas 52% favored more emphasis on prevention and 12% on treatment. Among those living in the West, those with higher levels of education and those with higher levels of income, 60% or more favored more emphasis on prevention.

Still more evidence of the American public's readiness for shifting the balance of our health care system away from treatment toward health maintenance appears in a 1978-1979 survey by Yankelovich, Skelly and White.[6] Again based on a national probability sample, 46% reported having "really changed their own and their families' life-styles—eating and exercise habits, etc.—in the interest of good health." Also pertinent to physician-patient partnership for health maintenance, 75% reported "a lot of confidence" in their doctors. On the other hand, 73% felt checkups cost too much for the average family, even though a strong majority perceived value in checkups—for adults as well as children.

A Schema for Health Maintenance

For several decades the American Medical Association (AMA) has been advocating "annual checkups." Although routinely espoused for the general population, standardized regimens for medical surveillance became popular only among certain groups, as indicated above, and the practice did not become widely established. Two factors may have contributed to the failure to attract adherence from the population as a whole. First, physicians did not achieve consensus on the contents of a checkup; many even remained skeptical of the value, especially in comparison with other components of their work, and their training did not prepare them for it, except in the case of obstetrics and pediatrics. Negativism prevailed despite the rhetoric of medical leaders. Second and perhaps more fundamental, the idea of an annual checkup did not make much biomedical sense. In the case of a pregnant woman, one stood a 25% chance of missing the whole episode! To achieve even adequate immunization of an infant, an "annual visit" was obviously insufficient. On the other hand, could one justify a checkup visit as often as once a year for a healthy man or woman 20 to 30 years of age? The issue of periodicity had to be faced.

During the 1970s a new approach to health maintenance emerged, called by some "lifetime health monitoring."[7] That approach was to specify periods of life—such as pregnancy; infancy; early and late childhood; adolescence; young, middle and late adulthood; elderly, and aged—for each of which physicians could set certain health goals and then outline professional services to reach these goals. For example, for persons 25 through 39 years of age health goals might be

- To prolong the period of maximum physical energy and to develop full mental, emotional and social potential.
- To anticipate and guard against chronic diseases through good health habits and early detection and treatment where effective.

Professional services

- Two professional visits with a healthy person—at about 30 and 35 years—including tests for hypertension, anemia, cholesterol, cervical and breast cancer and instruction in self-examination of breasts, skin, testes, neck and mouth.
- Professional counseling regarding nutrition, exercise, smoking, alcohol, marital, parental and other aspects of health-related behavior and life-style.
- Dental examination and prophylaxis every two years.

Various groups and persons have published such outlines. A rigorous evaluation of procedures to be included in periodic health examinations appears in a Canadian report.[8] The American College of Physicians has presented four schemata,

including the Canadian contribution.[9] A statement from the AMA Council on Scientific Affairs further illustrates the current recrudescence of the periodic health examination notion.[10]

Consensus appears to be developing that—by whatever name one prefers—lifelong health monitoring is a way to achieve a physician-patient partnership for health maintenance. The concept is to focus on preventing disease and promoting health. Its practice would encourage continuity of medical care, built around sensible periodic health appraisals already largely used for pregnancy and infancy and being used for limited groups of adults. It reflects a coherent view of health and the need for surveillance throughout life with attention to its biologic, psychological and social foundations. Lifelong monitoring of health aims at identifying two kinds of factors important to health: personal behavior in daily life; and physical variables, including anatomic, physiologic, chemical, immunologic, bacterial and genetic. Finally, it is designed to guide both physicians and patients toward preserving and even enhancing health.

Achieving the potential of lifelong health monitoring clearly requires that a patient and physician enter into a partnership, with wholehearted participation of both and respect for each other's role. Such an arrangement would be consistent with the several trends noted earlier.

Recent Experiences With Health Maintenance

The idea of moving away from medicine's almost exclusive focus on cure toward health maintenance, of course, does not imply jumping to the other extreme; proper balance is the goal.

Relatively great emphasis on third-party payment for hospital, surgical and medical services for treatment of sickness, along with denying payment for health promotion and preventive services, has long typified the American medical care scene. That policy reflected the original intent of insurance coverage—to pay for the cost of medical care to sick people. Insistence that payment for preventive services fell outside the range of insurance inhibited the development of such services.

Recently, however, the life and health insurance industry has begun to recognize the value of prevention. Lowering premiums to nonsmokers and showing its favorable economic impact opened the way.[11]

Initiation of the "life-cycle" project is a further step in that direction.[12] In that project, supported largely by the insurance industry, the introduction of systematic, carefully designed and monitored services in the lifetime health-monitoring mode is tested in three matched situations. Preliminary findings indicate the feasibility of that pattern of services, at least in group practices, paid for by insurance companies. Both patients and physicians expressed satisfaction, and the first data showed the average per-capita cost to be $59, ranging from $32 for preschool children to $135 for persons older than 75 years. Payment for counseling was included, but expenditures were kept low by eliminating tests regarded as unnecessary, such as routine chest x-ray films and electrocardiograms.

Similar attention to the benefits and cost of health-promotion services vis-à-vis regular medical services is leading industry, especially big firms, to introduce health-promotion activities for their employees at the work site. Frustrated by a failure to restrain the increased premium cost for health insurance, especially with no comparable improvement in benefits, many large corporations have turned to self-insurance. A number of such firms have also established health-promotion programs, to provide what seems a more obvious benefit for their employees. The extent of this development has thus far attracted little attention in medical circles. In California, a recent survey of employers with more than 100 employees at a site disclosed that, in addition to accident-prevention activities offered by 65% and training in cardiopulmonary resuscitation by 53%, from 8% to 19% had established programs against alcohol and drug abuse and for mental health counseling, stress management, fitness, hypertension screening and smoking cessation.[13] The number of such programs appeared to be rapidly accelerating.

Next Steps in Physician-Patient Partnership for Health Maintenance

Having briefly reviewed the basis in medical science, in medical practice and in public readiness for health maintenance as a new motif in health service, one may consider steps that might enhance a physician-patient partnership for that purpose. If achieved, it would constitute a considerable shift in emphasis for the work of physicians.

A fundamental step would be to introduce the necessary changes in physician education. In the predominant elements of current medical education—the principal exceptions being obstetrics, pediatrics and some family medicine programs—the role of physicians in health maintenance receives scant attention. Obviously in some specialties, particularly surgery and its components, substantial concern with that aspect of medicine would not be appropriate. The basic science curriculum, however, could be reoriented toward health maintenance. For example, many medical schools now offer a course in pathophysiology; why not some emphasis on "optimophysiology"? Training for medicine generally continues to stress diagnosis and treatment, especially of relatively rare conditions, rather than long-continuing relationships with patients devoted to health. Substantial reorientation of medical education would help prepare physicians to handle effectively the kind of physician-patient partnerships that are needed and developing.

Partnerships are, of course, two-sided enterprises, and complementary to physicians' role in health is that of the patients. Responsive to the American medical care situation in recent decades, people in this country have learned to look to physicians primarily for treating episodes of acute illness. One incidental outcropping of that experience can be seen in the tendency to use emergency rooms for care other than genuine emergencies. Although surveys indicate that people want more emphasis on health maintenance and prevention, they have not come to expect it of physicians. Perhaps that explains, in part, the tendency to seek help with alcohol problems, cigarette smoking, stress, diet and exercise outside the regular health care system. To establish a good physician-patient partnership for health, patients also must undergo some reorientation. In their case it involves both responsibility for health-related behavior and finding a physician relationship to guide and support such behavior.

However personally willing and ready physicians and pa-

tients may be for health maintenance service, the latter must also fit somehow into the system of health care. The people concerned may change the system, but as long as the system exists, it will determine how people behave in it. As long as the form of medical practice and the corresponding payment for its services include strong disincentives, health maintenance cannot thrive. Thus, organization of medical practice and appropriate payment mechanisms become necessary for health maintenance services to expand.

The growth of multispecialty group practice, which can support health maintenance logistically better than other forms of practice, and the willingness of the life and health insurance industry to consider explicit payment for it, are favorable signs. A physician-patient partnership for health maintenance is still an ideal to be achieved in medical practice.

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Some Obstacles to the Evaluation and Effective Performance of Health Appraisals

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Certain obstacles exist in evaluating screening tests and health examinations. When a voluntarily screened group is compared with an unscreened group and when the survival of cases detected in these two groups is compared, self-selection bias, lead-time bias, length bias and overdiagnosis confuse the evaluation and usually make an examination seem better than it really is. A randomized controlled trial overcomes these biases; one group is offered screening, the other is not and the outcomes in both entire groups are observed. Unavoidable crossovers between the groups tend to obscure any benefit of the examination, however. Evaluations of screening tests have tended to emphasize the value of positive results and have neglected the value of negative results. In obtaining maximum benefit from health appraisals, attention needs to be directed at self-selection, nonmedical threats to life and health, risk factors in addition to early disease and tailoring an examination to the needs of individual patients.

(Friedman GD: A critique of health appraisals, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:782-785)

The value of health examinations continues to be controversial. Prevention of disease, disability and premature death is a goal that, like peace, prosperity and morality, is almost universally desired. Yet, we know little about the contribution that health examinations make toward health and longevity relative to the effort and expense required. Furthermore, the optimal content and frequency of health checkups for various subgroups of the population are not well established.

The controversy rests partly on the scarcity of scientific data about health examinations and partly on a limited awareness of the problems associated with evaluating these examinations. These issues have been discussed in the epidemiologic and preventive medicine literature; this special issue provides a most appropriate setting in which to review several of these problems for readers with varied medical backgrounds.

In this article, two main topics will be discussed—biases frequently involved in the objective evaluation of health examinations and important epidemiologic issues that should be considered in the actual conduct of health examinations.

Problems in Evaluation

Health appraisals or components of them, such as screening tests, can be evaluated by two general types of epidemiologic study. One type, the observational study, entails a comparison of what happens to people who, on their own, either do or do not get these services. In the second type, the experimental study, an attempt is made to control the situation by defining at least two similar groups (preferably by random assignment) and giving the service to only one of them; the outcomes in the groups are then compared.

The experimental approach is very challenging because of difficulties in controlling human behavior to assure that an experimental design is followed—that is, that the service is received by most or all of those designated to receive it and by few or none of those in the comparison group. As a result, many evaluations have been observational.

At first glance it seems natural and appropriate to compare the examined or screened with the unexamined or unscreened. But several biases have been recognized in these observational comparisons, biases that will usually make an examination or screening test appear to be more desirable than it really is. Some of these biases are subtle and some not so subtle, as will be seen.

Self-selection Bias

One of the not-so-subtle biases is that of self-selection. When people decide for themselves whether they are to be examined, those who avail themselves of these services are not a representative cross section of the general population. It is now well recognized that participants tend to be of higher

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socioeconomic status, better educated and more health-conscious, and to have better health habits (such as less tendency to smoke and to drink alcohol to excess) than nonparticipants.[1,2] Then, too, some persons may not participate because of illness or poor health. Clearly, with respect to most health outcomes, the participants would do better than nonparticipants, even if the examination being evaluated is worthless.

This bias is nicely illustrated in the Kaiser-Permanente Multiphasic Evaluation Study.[3] This study was an experiment in which a middle-aged study group was urged to receive health checkups annually over a 16-year period and a control group was not so invited. Persons in the control group who, without any urging, came in for checkups as many times as persons in the study group generally had a much lower mortality rate. Consider, for example, the study group members and the control group members who came in for exactly three checkups. The death rate of these relatively resistant study group members (3 examinations despite as many as 16 urgings) was twice that of the self-motivated control group members (G. D. Friedman, MD, M. F. Collen, MD, B. H. Fireman, MA: "Multiphasic Health Checkup Evaluation: A 16-Year Follow-up," unpublished paper).

Self-selection does not always lead to bias in favor of an examined group. Breast cancer tends to occur more often in women of high than in women of low socioeconomic status. Also, women who have noticed suspicious breast lumps, which are sometimes cancerous, and women with a family history of breast cancer may be motivated to participate in breast cancer screening programs. In the case of breast cancer screening, then, a self-selected screened group probably will have more members who would eventually die of breast cancer than a self-selected unscreened group. This is illustrated by the randomized controlled trial of annual breast cancer screening conducted by the Health Insurance Plan of Greater New York. The rate of development of clinically apparent breast cancers was lower in the study group members who refused screening than in the entire control group who were not offered the annual screening.[4]

Lead-time Bias

The chief aim of health examinations of asymptomatic people is to detect disease early while treatment is still effective in postponing disability or mortality. For simplicity, let us focus just on mortality. What health screening is supposed to accomplish is to extend life. Early detection with no extension of life merely prolongs a patient's awareness of a serious disease and is probably a disservice to many persons. The problem in evaluation is apparent when we compare the survival of persons from time of diagnosis of a condition detected by screening in an early presymptomatic stage with the survival from time of diagnosis of persons whose disease is detected after symptoms develop. Even if screening has absolutely no effect on prolonging life it would *appear* to lead to longer survival merely because the disease was picked up earlier. The average interval between early detection by screening and ordinary clinical detection is known as lead-time (Figure 1). The lead-time for breast cancer screening by physical examination and mammography is about one to two years.[4] The effect of lead-time is to improve the apparent average survival time or five-year survival rate of a screened group, measured from the time of diagnosis, whether or not screening leads to prolongation of life.

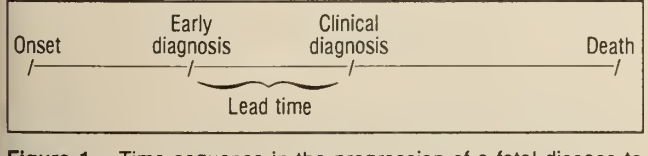

Figure 1.—Time sequence in the progression of a fatal disease to illustrate lead-time, which is the interval between early detection by screening and the usual clinical detection after symptoms develop.

Length Bias

Some cancers grow slowly and metastasize late whereas other cancers grow quickly and metastasize early. An examination at an arbitrary point in time is more likely to detect a slow-growing presymptomatic cancer than a fast-growing presymptomatic cancer. To illustrate this principle, Figure 2 shows an example that is simplified for the purposes of clarity. Each horizontal line above the bottom marker line shows the preclinical duration of a case that is either one year or three years. It is assumed that, at the beginning of each year, one 1-year case and one 3-year case occur and that screening could detect the disease at any time during the preclinical interval. The figure shows a 4-year window, with cases that preceded the window or lasted beyond the window indicated with dots. From the example, readers should confirm that during any year, if a screening program is carried out, three 3-year cases and only one 1-year case will be detected, even though the example was constructed so as to have equal numbers of 1-year and 3-year cases.

Consequently, a single screening program will preferentially pick up a slowly progressing over a quickly progressing disease. Cases detected by screening will therefore have a better prognosis even if screening leads to no beneficial consequences.

If a health screening program is repeated at frequent regular intervals, a more representative mix of new cases will be detected in the second and later sessions, after many of the slowly progressing cases are picked up at the initial

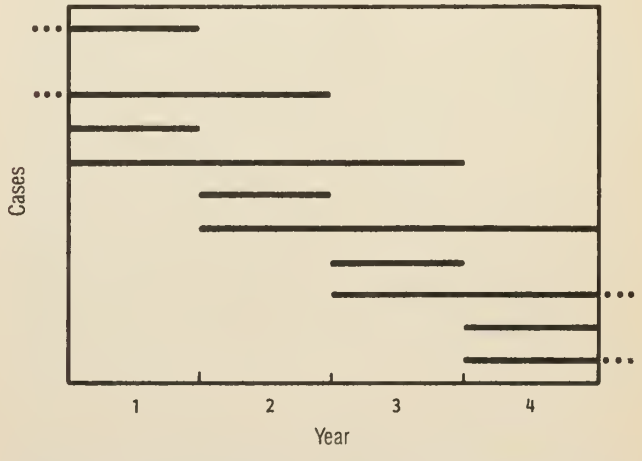

Figure 2.—Simplified example of an equal mixture of cases with short (one-year) and long (three-year) preclinical intervals, in which diseases are detectable, as the cases appear in a four-year window. If a screening program is carried out at anytime during the window, three cases with long and one case with short preclinical intervals would be detected.

screening. The frequent subsequent screenings ensure that a backlog of undetected slowly progressing cases does not build up.

Overdiagnosis

When a disease is actively looked for in asymptomatic persons, some of the cases that seem to be detected are misdiagnosed. The distinction between mild cases of the disease and no disease at all is often difficult to make. For example, a patient with a generally normal blood pressure may be found to have a mildly raised blood pressure at one or two office visits and erroneously be labeled as having hypertension. Some small breast lumps have cells that may appear malignant to a pathologist and a diagnosis of early cancer may be made when the lump is not cancerous at all. In a study of cervical cancer, a group of expert pathologists did not agree with the diagnosis previously made on 32% of 728 tissue biopsy specimens.[5] It was estimated that errors could have meant that up to one fifth of the resulting hysterectomies were unnecessary.

Consider a group of patients with a disease diagnosed as a result of preventive health examinations. If a substantial fraction of these patients does not actually have the disease, the survival and other health outcomes of this group are going to appear very favorable indeed.

Implications: The Need for Controlled Experiments

The four sources of bias just described—self-selection. lead-time, overrepresentation of slowly progressing disease and overdiagnosis—come into play particularly when an examination or disease-detection program is evaluated by an observational study in which the examined persons are compared with nonexamined and the survival of cases detected at the examination is compared with the survival of cases detected in the usual manner when symptoms develop. The effect is usually to make the disease-detection procedure appear more worthwhile than it really is.

These biases can be overcome if the evaluation is an experiment in the form of a randomized clinical trial. Two equivalent groups are identified by a random selection process and one of the groups is offered the examination to be evaluated. Then the outcome is measured in a comparable manner in both *entire* groups. By looking at each group in its entirety, self-selection becomes irrelevant because the cooperative and noncooperative are included in both groups. By looking at each entire group's mortality (or another endpoint) due to the disease(s) at which the examination is directed, the problems of lead-time bias, length bias and overdiagnosis are obviated because the comparison is no longer between the examined and unexamined. This type of randomized controlled trial answers the research question, "Did establishing a program to detect X disease lead to a lower mortality from X disease?" A classic study, which nicely fits this model, is the Health Insurance Plan of Greater New York's screening for breast cancer.[4]

Loss of Power in Experiments

As stated earlier, it is difficult to conduct large-scale experiments of this type in free-living humans. What usually happens is that some persons who are supposed to receive the examination being evaluated, some members of the so-called treated group, do not agree to receive it or do not show up when they are supposed to. Similarly, some members of the control group will seek out and receive the examination without any encouragement from the study. This leads to a "crossover" problem in which the treated and control groups become more similar to each other than is intended in the experiment. This in turn tends to make the outcomes of these groups more alike and to reduce the apparent benefits of the examination.

The Kaiser-Permanente Multiphasic Evaluation Study[3] provides a nice illustration of the problem. Members of the treated group, called the "study group," were urged to have a multiphasic health checkup every year. Members of the control group were not so urged but could avail themselves of this service as part of the care provided by the Kaiser-Permanente Medical Care Program. Each year only about 60% of the study group received the examination and at the end of 16 years, 16% had never received even one. About 20% of the control group came in on their own each year and after 16 years 64% had received at least one checkup. Although the "dosage" of checkups was higher in the study group than in the control group (mean of 6.8 versus 2.8 per person in 16 years, respectively) the considerable crossover problem is apparent.

When crossovers cause a study to lose power to detect and to show benefits of examinations, the investigators may be tempted to conduct additional comparisons within their study groups of the participants versus the nonparticipants. Even if done within a randomized controlled trial, such comparisons entail the same biases as described earlier for observational studies. These additional analyses may be interesting and lead to a better understanding of the phenomena under investigation, but they should not be regarded as the main results of the study. When there is considerable crossing over and the experimental group does little better than the control group, whereas the participants do much better than the nonparticipants, the truth probably lies somewhere between the results of these two comparisons.

The Value of Negative Test Results

Much of the evaluation of screening tests or procedures in health examinations has focused on positive test results. We want to know what the yield of a test is in terms of positive findings and how many of those who have positive findings turn out actually to have the disease being sought. Then we want to know the cost of the effort for each positive result and for each actual case detected.

Garfield has pointed out[6] that the patients who have negative results from a test also receive something of value in the form of reassurance, relief of anxiety and assistance in planning their lives. In a society in which health is one of our highest priorities and concerns, we should not disregard the importance and value of negative findings when we evaluate examination programs.

Considerations in Conducting Examinations

Self-selection

Self-selection bedevils not only the evaluation of examinations; it is also an important consideration in conducting examinations. When a physician does health appraisals on patients, or when a screening program is instituted in a

community, the intention is to do as much good as possible, and this means reaching as many people as possible who have the disease(s) being sought. Because of self-selection not everybody will be reached and, often, the persons examined are the ones who need it the least. Suppose we want to detect undiagnosed cancers or premalignant lesions of the mouth, throat and larynx. The persons in whom these conditions are most prevalent—that is, those who drink large amounts of alcoholic beverages and smoke cigarettes—are the people who are least likely to show up for an examination.

If physicians and public health professionals want to accomplish the most with health appraisals, ways must be found to reach those persons who would derive the greatest benefit from these efforts.

Recognizing Nonmedical Threats to Life and Health

Health care providers are trained to think medically—that is, to think of diseases. Other preventable causes of death and disability tend to be ignored, some of which exact a much greater toll of life and health than many of the diseases that concern physicians and patients so much. The most glaring example of our misplaced priorities concerns physical trauma. (The unfortunate term "accidents" tends to negate the possibility of prevention.) In 1982 in the United States the leading cause of loss of person-years of life before age 65 was "accidents and adverse effects," meaning largely physical trauma. This category of causes of mortality, which does not include suicide or homicide, accounted for 25% of person-years lost, whereas all cancers accounted for 19% and heart diseases for 17%.[7]

Inquiring about the use of seat belts and somehow persuading patients to wear them regularly would probably increase average life expectancy far more than all the routine physical examinations done on patients younger than age 40.

Attention to Risk Factors

Checkups tend to focus on early detection of disease. However, patients may be free of diagnosable disease yet be at high risk of serious disease developing later on. Epidemiologic studies have repeatedly shown the existence of major risk factors for coronary heart disease including raised serum cholesterol levels, hypertension, cigarette smoking, obesity, diabetes mellitus, family history and lack of exercise. It is standard practice to actively intervene when unmistakable hypertension or diabetes mellitus is apparent; however, a person who has moderate elevations of several of these factors and who may be at just as high a risk of heart attack as someone with just one dramatic elevation may be neglected. A sedentary, moderately obese middle-aged man who smokes and has a serum cholesterol level of 260 mg per dl and a blood pressure of 150/90 mm of mercury needs our attention.

Fortunately, more and more physicians caring for adults are following the lead of their pediatric colleagues in trying to prevent as well as treat disease.

Tailoring the Checkup to the Needs of a Patient

Although authoritative groups and other experts have recommended specific content and frequency of health examinations,[8-12] all recognize the need for clinical judgment in altering checkups to meet the needs of individual patients. It is obvious that women who have never been sexually active do not need Pap smears as often as other women and that if a tuberculin-negative patient is possibly exposed to tuberculosis, periodic skin testing should be included in his or her examination program. Persons with a history of rectal polyps should have sigmoidoscopic examinations more often than those with no such history. These are just a few examples of the need to consider a patient's history and environmental exposures in deciding on the content and frequency of various health appraisals and procedures. Good judgment in these matters requires up-to-date knowledge about the risk factors and the natural history of diseases.

Such tailoring will increase health-care costs for some patients but can cut costs for others by avoiding or delaying tests that are not needed.

The Value of a Thorough Examination

Few examination procedures and screening tests have been proved effective in reducing disability and mortality when used routinely.[12] Nevertheless, at certain times, such as when a patient comes under the care of a new provider, a thorough examination is of great value. Certain conditions that, in healthy persons, need only be sought once (such as rheumatic heart disease in young adults, by history and cardiac auscultation) should be included as targets in these thorough examinations and need not be routinely pursued again. Baseline data collected from an asymptomatic person at a thorough examination (for instance, an electrocardiogram for comparison with later ones if cardiac symptoms develop) can be very useful. Taking an adequate medical and social history helps to establish rapport between patient and provider.

Patients appreciate thoroughness, too, and for this reason health-care providers and planners should exercise care in reducing established examination procedures solely in the pursuit of economy. Cost reduction is certainly much needed in health care today. Nevertheless, if reductions are made without explanation and patients believe that they are receiving a cursory examination, there will be other costs stemming from the reduced assurance that the examinations provide.

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The Cost-Effectiveness of Health Checkups—An Illustrative Study

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An economic analysis of personal health maintenance is complicated by the great variability in the health care process, the large amount of missing data and the great range in analytic results. Accordingly, this study should be considered more illustrative than conclusive. Data are available on middle-aged adults that periodic health checkups can be effective in significantly lowering mortality from potentially postponable disease. Using these data, a net-cost analysis has been attempted for periodic health checkups. The findings suggest that their costs and effects on health depend on how they are provided, how often and to whom. Yet, periodic health checkups can reduce lost earnings capability of examinees and can be cost-effective by using efficient health examination methods. If policy decision makers require health checkups for the lowest income people to be cost-effective, then these checkups probably will continue to be limited to case finding by physicians as an expense already included in current medical practice.

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Personal health maintenance, for the purposes of this economic analysis, is considered to include two groups of professional health care services—namely, health promotion and health status evaluation.

Health promotion involves health education and counseling to encourage persons to better their health through an improved life-style. Traditionally, primary care physicians include some health education and counseling in their routine patient care. Formal organized health promotion programs often include counseling for stress, smoking cessation, nutrition or weight reduction and improved physical fitness. These are usually carried out by nonphysician health care providers.

Health status evaluations (also called general physical examinations, health checkups, multiphasic checkups, health appraisals or case findings) are used to monitor a person's health, to identify high risks for specific diseases and to detect early abnormalities. Groups at high risk are those in whom the frequency of disease is demonstrably higher than in the general population. Disease is detected through health checkups or case finding. A health checkup is a group of procedures and tests provided to a presumably well person and generally includes a medical history, a general physical examination and supplemental laboratory or radiology procedures (or both), selected to determine the risk of future disease or to identify common important diseases still in their asymptomatic state. Health checkups are usually provided by physicians or by trained nurse practitioners or physician assistants working under physician supervision. Systemized approaches, such as multiphasic health checkups, sometimes involve automated procedures and technicians to collect data on patients' histories, laboratory tests and physiologic measurements in a programmed sequence.[1-3] Case finding includes supplemental health checkup test procedures during the medical examination or diagnostic workup of patients having one or more specific medical complaints or problems. Thus, case finding involves waiting for sick people to seek medical care and then providing additional testing procedures for the detection of selected potentially postponable conditions. Periodic health checkups usually are the primary basis for personal health maintenance programs; they consist of health protection plans that include test packages appropriate for different age groups.[4-7]

A test is considered appropriate if it has a high predictive value when positive—it has a high sensitivity for identifying a possibly disabling disease occurring with a relatively high prevalence, and a high specificity for identifying persons without the disease—and if there is available an efficacious treatment for the disease.[8]

The effectiveness of a health program is generally expressed as the extent to which its intended objectives are actually achieved. The effectiveness of periodic health checkups can be assessed by such patient outcome measures

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as morbidity, disability and mortality. The most reliable method for measuring effectiveness is by a randomized controlled study.[9]

Costs for personal health maintenance services are usually established by individual health care providers who receive fees from patients as payments for these services, since personal health maintenance services are rarely covered by medical insurance programs.

Accordingly, health checkups may be included in case finding, whereby their costs then become reimbursable by third-party health insurers as services associated with a patient's medical complaints. Thus it is probable that many persons are already receiving such personal health maintenance services and their costs are already contained (but not identifiable) in the overall medical care costs. Health maintenance organizations provide many of these services on a prepaid basis and, when health checkups are included as a covered benefit, these costs can then be separately identified.

Many economists regard preventive medical services as an investment in health because they expect such services to increase the health of persons and reduce the future cost of medical care for some illnesses.[10]

Methods

An economic analysis of personal health maintenance services requires determining their costs. These costs will depend on the specific process used for providing these services—that is, whether a physician or a nonphysician health care provider, in solo or group practice—and the financing mechanism for paying for these services—that is, fee-for-service, cost reimbursement or prepaid insurance. It is often very difficult to establish true costs because charges (fees) of physicians and hospitals do not necessarily reflect actual costs.[11] Total costs should contain both direct and indirect costs. Direct costs include payments to hospitals and physicians; indirect costs include overhead expenses. For patients' costs, not only payments for services should be considered, but also patients' loss of earnings from being absent from work.[12-19]

In projecting future costs and benefits, estimates must be made for the effects of economic inflation by adjusting for a projected inflation rate. For long-term cost projections, low inflation rates tend to favor programs such as personal health maintenance whose major benefits tend to accrue in the distant future.[20-22]

The comparative effectiveness of alternative medical procedures can be best evaluated through randomized controlled studies; the data from such studies then permit a cost-effectiveness or a cost-benefit analysis.[17,19,20]

A cost-effectiveness analysis is a comparison of the costs and effects from alternative methods directed to achieving the same objective, for example, comparing the dollar expenditures and the effects on health of persons receiving a formal program of personal health maintenance with persons not receiving such a program. In a cost-benefit analysis, all the expenditures of alternative programs are compared with all the benefits derived. This requires reducing the value of all benefits to similar monetary terms (such as dollars) including, for example, the value of extended years of life. The value of a year of life is often defined as the average earnings of a person during a year.[13,14] Quantifiable measures of all relevant inputs and outputs to health care programs are not obtainable, so that incremental changes in health status resulting from additional services received are generally the most useful form of economic analysis. In such a study of personal health maintenance services, the additional costs of providing these specific services should be considered, as well as the resultant effects of these services on patients' outcomes.

Because all the definitive data required to carry out a cost-effectiveness analysis are usually not available, a series of assumptions must be made for the important variables and then various scenarios projected that provide a "sensitivity" analysis. Thus, one can test how sensitive are the analytic results to possibly important variations in the data used, and thereby attempt to decrease the range of uncertainty in policy-making decisions.[21]

Because health education and counseling are usually an integral part of traditional patient care by health care providers, it is difficult to estimate accurately the separate costs for these two services. The patients' outcomes from such health promotion components are usually expressed in terms of measured behavioral and life-style changes. Thus, measuring costs and benefits for health education programs is very difficult,[10,23] and an economic analysis of the health promotion component of a personal health maintenance program will not be attempted herein. Also, I will not attempt to evaluate the issues of patient compliance with recommended follow-up procedures, the value of reassurance to an anxious patient that a suspected disorder is not present and social costs such as the adverse effects of "labeling" persons found to have abnormalities.[24]

From the viewpoint of a health care policymaker, the cost-effectiveness of periodic health checkups, which generally serve as the basis for personal health care services, depends on the age of the examinees (older persons have different and more abnormalities than the young); the selection of low-cost tests with a high sensitivity for detecting abnormalities and high specificity for identifying persons who do not have the abnormality; the selection of potentially disabling abnormalities with enough prevalence to provide an acceptable cost per true-positive case; the availability of treatment to effectively decrease morbidity, disability and mortality; the intervals between repeat health checkups, and the earning capacities of the examinees.[7]

A useful economic analysis for a preventive program is the net cost, calculated as the costs of the program of examinations plus follow-up medical care, minus the reduction in medical care expense due to a decrease in disease incidence or severity, or both, and the increased income due to lengthened life expectancy and reduced work absenteeism. In such studies disease detection programs for hypertension[16] and for colon cancer[16,25] have reportedly been very cost-effective. In some industries, providing periodic health examinations to company employees has been cost-effective and resulted in substantial net earnings to the company.[26,27] Similar favorable findings were reported for life insurance policyholders.[28]

A Net Cost Analysis

A cost analysis of two alternative health checkup methods was done in which similarly selected patients receiving either a traditional or a multiphasic health checkup were compared.[29] A multiphasic health checkup consisted of a system-

TABLE 1.—*Summary of Total Costs per Patient for a Health Evaluation (Initial and Follow-up Procedures) Adjusted for Age, Sex and Health Status* *†

	Traditional	*Multiphasic*
Physician visits	$ 79	$44
Multiphasic laboratory	0	35
Clinical laboratory	32	5
X-ray studies and other	13	5
Total	$124	$89

*Modified from Collen et al.[29]
†Adjusted to 1984 dollars.

ized battery of tests and a self-administered medical history, followed by a 15-minute scheduled visit for a physical examination by a physician in the medical department. A "traditional" health checkup was provided by one of the same medical department physicians who, during a 30-minute scheduled visit, took a history, did a physical examination and arranged for supplemental diagnostic tests and procedures as indicated. After the physician saw a patient, in either a traditional or a multiphasic initial examination visit, the physician could refer the patient to appropriate follow-up specialty clinics or for clinical laboratory tests, x-ray films, electrocardiograms or other special procedures as necessary to confirm the presence or absence of a suspected condition. The resultant patient group data were adjusted so as to be comparable by age, sex and health status. Because the same physicians provided all the examinations and the follow-up care for both groups, the quality of professional care was assumed to be similar.

From this study,[29] the total costs (adjusted to 1984 dollars) for providing health checkups by the two methods were compared (Table 1). These costs are calculated to be the actual expenses to the Kaiser-Permanente medical care program, a prepaid group practice health maintenance organization, and do not represent fees or charges to patients. The total cost for a health checkup is the sum of the resources used in the initial examination visit and in the follow-up visits required to complete the health status evaluation of a patient. The data show that the average cost for a health evaluation by a traditional physician examination and follow-up in 1984 would be $124. As an alternative, by first providing multiphasic health testing followed by a physician examination, the total costs for a health evaluation in 1984 would be $89, or a decrease of 28%.

Many studies have been done evaluating the effectiveness of individual tests and procedures for detecting specific diseases, but the results of only one long-term, randomized controlled study of periodic health checkups have been published.[24,30] A group of more than 5,000 adults (aged 35 to 54 years at entry to the study) were urged to have a multiphasic health checkup annually, a comparable control group was not so urged and both groups received their follow-up care from the Kaiser-Permanente medical care program. After 11 years, about 70% of both the study and the control groups remained in the program. A study of mortality rates showed that, compared with the control group, after seven years the study group had had a 50% reduction ($P < .025$),[31] after nine years a 36% reduction ($P < .05$)[24] and after 11 years the study group still showed a 35% reduction ($P < .05$)[32] in deaths from prespecified "potentially postponable" conditions, largely due to lower death rates from colorectal cancer and hypertension (Table 2). Because all persons eventually die, it can be expected that the differences in mortality between these two groups will steadily decrease in time. It was not expected that other causes of death that were not preventable or postponable would be affected by these checkups.

Because it is uncertain to what extent these data for costs and patient outcomes are transferable to another environment and projectable into the future, it is useful to decide on a likely range for these important variables to attempt to decrease the uncertainty of decision makers and reduce the risk of a bad decision. Accordingly, a sensitivity analysis has been done using what are considered to be realistic values for the next ten years. Ranges are then defined as to what might be optimistically the best case and pessimistically the worst case. Three "optimistic," "realistic" and "pessimistic" scenarios can then be developed.

Assume that 1,000 adults, ages 35 to 54 years, follow the Kaiser-Permanente experience.[24,30-35] Assume optimistically that they would follow the study group model and receive, on the average, five checkups in ten years (that is, one in 1984, 1986, 1988, 1990 and 1992), that realistically they would follow the control group's experience and average two checkups in ten years (for instance, one in 1987 and a second in 1990) and that pessimistically they would take only one checkup in the next ten years (that is, only in 1988). Table 3 shows the data for the group with one checkup in ten years extrapolated from the other two groups.

Based on the Kaiser-Permanente randomized controlled study, it can be projected that the number of deaths at the end of ten years from colorectal cancer will be 1.0 for the optimistic group—that is, with five checkups in ten years—and 3.3 for the realistic group—that is, with two checkups in ten years. We then extrapolate 5.0 deaths for the pessimistic group. Similarly, it can be projected that the number of deaths from hypertensive disease at the end of ten years will be 2.5, 4.7 and 8.0, respectively, for these three groups.

The following (1984) dollar costs are then assumed (also based on Kaiser-Permanente data), as shown in Table 3. The average cost for a complete health checkup is assumed to be optimistically (by a systemized multiphasic checkup) $90, realistically (by the traditional physician checkup or case finding) $125 and pessimistically $250. Of course, the range of costs for checkups, as well as for the other medical costs that follow, may be much greater than these averages.

For the purposes of this analysis, it is assumed that the only significant differences in mortality due to periodic health checkups were in two potentially postponable conditions, colorectal cancer and hypertension, and all medical care calculations are based on these two differences. From a review of the Kaiser-Permanente medical records of terminal cases in the reported controlled study, the average total medical costs for a case of colorectal cancer are estimated to be about $12,000, resulting from about 20 physician office visits, 25 hospital days, major abdominal surgical procedures, multiple endoscopy and x-ray procedures and many clinical laboratory tests. Accordingly, a realistic cost for a terminal case of colorectal cancer is considered to be $12,000, an optimistic figure is assumed to be $8,000 and a pessimistic cost is assumed to be $20,000. For a case of colorectal cancer detected early by checkup in which the patient does not die, the medical care costs are estimated to be about a fourth that of a terminal case.

For hypertensive patients who died of congestive heart failure, myocardial infarction, stroke or renal failure, the review of actual case records showed a great variance in the course of the disease. Some patients died suddenly of a massive cerebral hemorrhage and incurred minimal medical care costs, whereas others received many years of medical care including many admissions to hospital for congestive heart failure and accrued very large medical care costs. It is assumed, for this economic analysis, that optimistic, realistic and pessimistic medical costs for the care of terminal hypertensive disease averages $6,000, $10,000 and $18,000, respectively. The medical care costs for the treatment of cases of hypertension detected earlier and in which the patients did not die were essentially only from extra office visits for a relatively small number of patients; they would not affect the costs significantly and were not included.

The earnings capability of a person, when such is lost due to illness, is an important cost to a patient and essential to consider in projecting long-term costs for a health program.[20] Earnings capability for a housewife are often imputed by courts at some contemporary value.[13] Accordingly, Table 3 assumes a realistic average earnings capability for all middle-aged persons in 1984 at $25,000, optimistically at $50,000 and pessimistically at $10,000.

Projecting future economic inflation rates is hazardous and the long-term cost-effectiveness of a procedure or program is very sensitive to the rate of inflation. For this economic analysis, the same inflation rates are applied to both projected costs and earnings. An average annual inflation rate over the next ten years is assumed to be realistic at 6%, optimistic at 3% and pessimistic at 10%.

Using all of the values shown in Table 3, the appendix of this article shows the calculations associated with the generation of various scenarios and their projected ten-year costs (see Table 4).

Discussion

This economic analysis shows how complex it is to attempt to use formal cost-effectiveness studies for health care due to the unavailability and uncertainty of analytic data, which can produce a great range of results. Also in this study the issues of patient compliance with recommended follow-up procedures, the value of reassurance to an anxious patient that a suspected abnormality is actually not present and social costs such as the adverse effects of labeling persons found to have abnormalities were not considered.[24] There are alternative methods with different costs for providing health checkups; the costs and outcomes are very sensitive to the interval between checkups. The scenarios in Table 4 show that at the same realistic unit costs, changing from five checkups in ten years (scenario V) to two checkups in ten years (scenario IV), or to only one checkup in ten years (scenario III) considerably reduces the total costs expended for checkups (from $775,000 to $315,000 to $153,000 over ten years). However, the costs for care of patients with colorectal cancer or hypertensive disease are substantially increased (from $54,000 to $113,000 to $177,000) with the associated increased loss of total earnings capability (from $550,000 to $1.26 million to $2.05 million). If a scenario were generated for those never receiving any checkups at all in ten years, these differences could be even greater.

Because scenarios III, IV and V are similar in that they all use the same realistic unit costs and inflation rate, the effects of receiving health checkups only once, twice or five times in ten years can be compared by calculating annual net cost per life saved. Scenario V with five checkups in ten years versus

TABLE 2.—*Death Rates per 1,000 in Study and Control Groups, After 7, 9 and 11 Years**

	After 7 Years†		*After 9 Years‡*		*After 11 Years§*	
	Study	*Control*	*Study*	*Control*	*Study*	*Control*
Potentially postponable causes	3.7	7.4‖	6.8	10.7¶	8.6	13.2
Cancer of colon and rectum	0.4	1.8¶	0.6	2.5¶	1.0	3.3
Hypertension and hypertensive cardiovascular disease	0.6	2.2¶	2.0	4.0	2.5	4.7
All causes	35.6	39.2	53.7	55.1	68.7	71.0
Average number of examinations	3.5	1.3	4.5	1.7	5.2	2.0

*Populations as of January 1, 1965; study, N = 5,138; control, N = 5,536.
†Modified from Dales et al.[31]
‡Modified from Friedman.[24]
§Modified from Dales et al.[32]
‖$P < .025$.
¶$P < .05$ (χ^2 test).

TABLE 3.—*Assumptions of Possible Variations in Important Variables*

Variable	*Projected Scenario*		
	Optimistic	*Realistic*	*Pessimistic*
Checkups in 10 years	5	2	1
Average deaths per 1,000 after 10 years from			
Colorectal cancer	1.0	3.3	5.0
Hypertensive disease	2.5	4.7	8.0
All potentially postponable conditions	8.6	13.2	18.0
All causes	68.7	71.0	73.0
Average cost (1984 $) per			
Health checkup	90	125	250
Terminal colorectal cancer case	8,000	12,000	20,000
Terminal hypertensive disease case	6,000	10,000	18,000
Average annual earnings capability (1984 $)	50,000	25,000	10,000
Average annual inflation rate (%)	3	6	10

TABLE 4.—*Projected 10-Year Costs ($) for 1,000 Adults Under Various Scenarios*

	Scenario Variables						
	Checkups in 10 yrs	*Patient Outcome*	*Projected Costs*	*Total Checkup Costs*	*Medical Care Costs**	*Total Program Costs*	*Lost Earnings Capability**
I.	1	Pessimistic	Pessimistic	$355,386	$357,242	$712,628	$ 951,665
II.	5	Optimistic	Optimistic	493,482	33,386	526,868	984,813
III.	1	Pessimistic	Realistic	153,234	176,750	329,984	2,051,530
IV.	2	Realistic	Realistic	315,449	113,119	428,568	1,262,480
V.	5	Optimistic	Realistic	775,365	54,713	830,078	552,335

*For cases of colorectal cancer and hypertensive disease.

scenario IV with two checkups in ten years results in a saving over ten years of 4.5 lives from potentially postponable conditions—colorectal cancer and hypertensive disease—at an increased cost of $459,916 for health checkups but at a saving of $58,406 in medical care costs for these cases. Total medical program costs (for checkups and medical care) are shown in Table 4 for scenario V as $830,078, or $401,510 greater than for scenario IV. However, scenario V shows a reduction in lost earnings compared with scenario IV of $710,145, for a net ten-year overall net saving of about $300,000 to the community for the medical care program and the patients, in addition to the 4.5 more lives saved.

Scenario III, with only one health checkup in ten years, saves $622,131 over ten years for health checkups compared with scenario V, but spends $122,037 more in ten years in medical care costs for colorectal cancer and hypertension cases. Total medical program costs for scenario III are only $329,984. However, checkups only once in ten years, compared with checkups every other year, lose for these patients $1,499,195 in earnings capabilities over ten years. Accordingly, scenario V net cost compared with scenario III for ten years is almost $1 million less and saves 9.5 more lives.

Assuming scenario V were modified to use a systemized multiphasic type checkup at a $90 unit cost in 1984, then total ten-year costs for checkups every other year would be similar to that for scenario II and medical care costs and lost earnings would be similar to that of scenario V. Thus ten-year total program costs would be about equal to the ten-year lost earnings capability. Although ten-year total program costs for modified scenario V with multiphasic checkups would remain about $200,000 greater than for scenario III, ten-year total lost earnings would remain $1,499,195 less. This would result in a ten-year overall net saving of about $1.25 million and 9.5 more lives saved.

For persons with average annual earnings of less than $10,000, it is only possible to balance the overall net costs by decreasing the costs for health checkups. Thus, it is evident that periodic health checkups can be a cost-effective basis for personal health maintenance depending on who receives them and how the tests are selected and furnished. They easily can be made cost-effective by selecting high-income examinee groups and providing systemized multiphasic type checkups, which include low-cost test procedures for high-risk potentially postponable conditions. Does that mean that saving the lives of persons from very low-income groups is not as beneficial? Decisions on such issues by health care policy makers are often made on a sociopolitical basis.[20-22]

Because an economic type of analysis is most useful for cost-containment decisions, it is limited in its ability to help with health care policy decisions, as valid quantitative measures of effects and benefits on quality of care are not available and the validity of estimating any such variables used is controversial. Similarly, social values, ethical considerations and political realities may well take precedence over analytic economic results. The Congressional Office of Technology Assessment (OTA) has noted that the conflict between equity and efficiency is an important issue in the use of economic analysis; it cites the difficulty in measuring a person's worth, assigning value to equality, fairness and justice and of valuing the quality of extended years of life.[20] OTA has also pointed out that economic analysis has had little relevance to decision making in medical practice because its primary focus is cost-effectiveness from a societal or policy-making viewpoint. In addition, because a physician's major responsibility is to patients, the perspective of a physician may be different from that of a policy maker or of a patient. From the viewpoint of a patient, does one seek a health checkup because one thinks it is cost-effective, because one wants reassurance and peace of mind or because it is required for some reason? It is unlikely that most persons buy a health checkup with the purpose of gaining quantifiable benefits.

Even though the cost-effectiveness of health checkups may not be demonstrable to everyone's satisfaction, a significant percentage of Americans is already for various reasons receiving health evaluations, medical checkups, case finding, employment examinations and physical fitness appraisals. Many are following the model set by government officials, generals and industry executives for periodic health evaluations. It is not possible to isolate expenditures for personal health maintenance services in the course of physician office visits, but these expenses are already built into our nation's overall health care costs. If medicare and health care insurers all paid for periodic health checkups, then the costs for these personal health maintenance services could be better identified.

Appendix

I. A Pessimistic Scenario

Using the assumed "pessimistic values" shown in Table 3, the projected cumulative costs for ten years for 1,000 middle-aged adults can then be estimated as follows:

1. The cost per checkup at a 10% average annual inflation rate in 1984 is $250 and in 1988 would be $366.
2. The number of examinees (assuming 7.3 deaths per year from all causes and all survivors have one checkup) in 1984 is 1,000 and in 1988 would be 971.
3. The average costs for checkups in a ten-year period are $366 × 971 = $355,386.

4. The costs for terminal cases of colorectal cancer and hypertensive disease: Assuming average costs of care for colorectal cancer in 1984 are $20,000, at an average rate of 10% inflation, the average cost for colorectal cancer for the ten-year period is $29,282. For five terminal cases of colorectal cancer in the ten years, the ten-year costs of care are $146,410. Assuming the average costs of cases of hypertensive disease in 1984 are $18,000, at an average annual inflation rate of 10%, the average cost for a hypertensive case in the ten-year period would be $26,354. Then for 8.0 cases of terminal hypertensive disease in ten years, the total ten-year costs would be $210,832. The total ten-year costs for both colorectal cancer and hypertensive disease would be $357,242.
5. Assuming a pessimistic average earnings capability in 1984 to be $10,000, at a 10% average annual inflation rate, the average earnings in 1988 would be $14,641. Again, assuming all terminal cases to be evenly distributed, the average cumulative projected earnings of each would be $14,641 × five years = $73,205. For 13 cases, the cumulative projected earnings lost due to deaths from colorectal cancer and hypertensive diseases would total $951,665.

II. An Optimistic Scenario

Using the assumed "optimistic" values shown in Table 3, the projected cumulative costs for ten years for 1,000 middle-aged adults would then be as follows:

1. Cost per health checkup, at 3% annual inflation rate, in 1984 would be $90.00; in 1986, $95.48; in 1988, $101.29; in 1990, $107.46, and in 1992, $114.00.
2. The differences in death rates from all causes shown for optimistic and pessimistic scenarios in Table 3 are slightly less than the differences for deaths from possibly postponable causes. The use of either will not significantly affect this net cost analysis. Accordingly, the number of examinees, assuming 6.87 deaths per year from all causes as shown in Table 3 and that all survivors have checkups, will be 1,000 in 1984; 986 in 1986; 973 in 1988; 959 in 1990, and 945 in 1992.
3. Annual costs for health checkups:

1984	= $ 90.00	× 1,000	=	$ 90,000
1986	= 95.48	× 986	=	94,143
1988	= 101.29	× 973	=	98,555
1990	= 107.46	× 959	=	103,054
1992	= 114.00	× 945	=	107,730
Total ten-year checkup costs			=	$493,482

4. Total costs for care of cases of colorectal cancer and hypertensive disease—assuming the average cost for care of a patient with terminal colorectal cancer in 1984 is $8,000, at 3% annual inflation rate—in 1988 will be $9,004 for one case. Compared with scenario I, the care for four colorectal cases in which disease was detected early and the patients did not die will be $8,000. The average cost for care of hypertensive disease in 1984 is $6,000; at a 3% annual inflation rate, in 1988 it will be $6,753; for 2.5 cases, $16,882. The total ten-year costs for care of cases of colorectal cancer and hypertensive disease would be $33,886.
5. Assuming the average optimistic annual earnings capability for survivors in 1984 is $50,000, at a 3% average annual inflation rate, in 1988 it would be $56,275. Assuming the terminal cases were evenly distributed during the ten-year period, the average patient would earn $56,275 a year × five years = $281,375. For 3.5 cases, the cumulative projected earnings lost due to deaths from colorectal cancer and hypertensive disease would total $984,813.

III. A Pessimistic-Realistic Scenario

In scenario III of Table 4, ten-year costs are projected for a similar group receiving only one health checkup in ten years, with the associated pessimistic patient outcomes shown in Table 3, yet holding all unit costs at realistic values and a 6% inflation rate. The calculated total ten-year costs for health checkups would be only $153,234, but the total medical care cost for cases of colorectal cancer and hypertensive disease would be $176,750 and their cumulative lost earnings would total $2,051,530.

IV. A Realistic Scenario

Following the same method and using the "realistic" values shown in Table 3, the projected cumulative costs for ten years for 1,000 middle-aged adults would then be as follows:

1. The cost per checkup at a 6% average annual inflation rate would be in 1984, 1987 and 1990, respectively, $125.00, $148.88 and $177.32.
2. The number of examinees (assuming 7.1 deaths per year from all causes and that all survivors have checkups) would be in 1984, 1987 and 1990, respectively, 1,000, 979 and 957.
3. The costs for health checkups in 1987 and 1990 would be $145,754 and $169,695. The total ten-year checkup costs would be $315,449.
4. The costs for cases of colorectal cancer and hypertensive disease are as follows: Assuming the average cost for colorectal cancer in 1984 is $12,000, at an average annual inflation rate of 6%, the average cost for a colorectal cancer case in the ten-year period would be $15,150. For 3.3 terminal cases of colorectal cancer, the total ten-year care costs would be $49,995. For 1.7 cases of colorectal cancer detected early and in which the patients did not die, the costs would be $3,788. Similarly, assuming the average cost for hypertensive disease in 1984 is $10,000 and the average annual inflation rate is 6%, then the average cost for a case of hypertension in the ten-year period would be $12,625. For 4.7 cases of terminal hypertensive disease, the ten-year costs would be $59,336. The total ten-year costs for cases of both colorectal cancer and hypertensive disease would be $113,119.
5. Assuming the average realistic annual earnings capability for survivors in 1984 is $25,000, at a 6% annual inflation, the average earnings in 1988 would be $31,562. Assuming an even distribution of deaths over ten years, each would accumulate total earnings averaging $31,562 a year × five years = $157,810. The cumulative projected earnings lost due to eight deaths from colorectal cancer and hypertensive disease would total $1,262,480.

V. An Optimistic-Realistic Scenario

Similarly, scenario V in Table 4 can be projected for 1,000 middle-aged adults who receive health checkups every two years with the associated optimistic patient outcomes, yet holding all costs for checkups and medical care services at realistic unit costs and 6% inflation per year (from Table 3). Table 4 shows that the total health checkup costs for ten years would equal $775,365; the medical care costs for cases of colorectal cancer and hypertensive disease would total $54,713, and the average cumulative lost earnings for these terminal cases would total $552,335.

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Societal Influences on Health and Life-styles

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Strong sociocultural forces affect individual attitudes toward health and choice of life-style. Economic deprivation fosters negative health behaviors. Positive health habits are reinforced by discrete societal groups. The news media, particularly television, disseminate much useful health information, though the overall educational value is diminished by the content of commercial messages and programming. The automobile is a major societal influence, but neither individual drivers nor the car manufacturers give enough priority to highway safety, leaving that role to governmental regulation. American industry is becoming a positive influence in the encouragement of good health habits, and fashion is lately an important ally in personal health maintenance.

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There is now abundant evidence that control of many major health problems in the United States will require modifying individual behavior and the daily habits of living. Data supporting this assertion, gathered over many decades, have been emphasized in the recent medical literature and lay press and are discussed from a number of different perspectives in this issue. Clearly, progress in defining and quantifying health risks has been impressive and increasingly provides an authoritative basis for recommending personal health practices that promise a greater likelihood of longer life. However, the notions that nutritious food, regular exercise, adequate sleep and weight control help to prevent disease while smoking cigarettes, failing to wear seat belts, drinking too much liquor and driving fast may shorten life are not really new to either physicians or most of their patients. The problem is that so many of us ignore this information and persist in following harmful life-styles. It appears that the health of the nation suffers because too many persons simply refuse to accept the responsibility for taking proper care of themselves.[1]

Of course, it is not quite that simple. True, Americans take great pride in the exercise of individual determinism—that is, the ability of people to shape their own lives. Granted that within certain limits each person does have a great deal to say about how he or she lives, individual behavior is greatly influenced by social forces. The thoughts, feelings and, ultimately, actions of each person are molded to a major degree by the culture in which that person is reared and educated. For this reason, individual attitudes toward personal health matters, like other attitudes, reflect societal perceptions of what is important.

In the past, health attitudes and practices were often based on deeply held values about the nature of humans and life, usually expressed as religious beliefs and rituals. Thus, according to Herodotus, the ancient Egyptians, fearful of the morbid consequences of intestinal putrefaction, purged themselves for three successive days each month with emetics and enemas.[2] This emphasis on bowel hygiene was passed along to the Greeks, thence into western health practices, persisting even into modern times (such as the "high colonic"). In Epicurean Rome, where cleanliness was virtually a religion, the daily bath became an important element in personal health maintenance.[3] The great public baths of Caracalla and Diocletian accommodated as many as 3,000 citizens at a time. Vigorous exercise such as boxing, wrestling, running, jumping and playing ball usually preceded a relaxing interval in a steam room and the bath itself. The giant Roman thermae were, in fact, the first hydrotherapeutic institutes for maintaining health and reducing stress. This essential concept was resurrected during the past century as elaborate spas in Europe and is again fashionable today in the form of urban health clubs and posh "health farms."

While science now provides a more rational basis for choosing a healthy life-style than was available to the ancients, individual behavior is not predicated on the best available scientific evidence. Hence, one may fairly ask what societal forces now operate to influence a person's choice of health habits. In particular, why does our present society fail to inculcate in more persons a deeper sense of responsibility for their own well-being?

Human behavior is the composite reflection of a multiplicity of sociocultural factors acting on a biologic substrate,

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and our understanding of most of the variables is primitive. Some important societal influences on health behavior can be singled out, however, and deserve our attention because, in principle, these influences can be changed for the better.

Sociocultural Factors

In 1983, according to a special report, 29 million Americans, 12% of the population, were considered to be medically disadvantaged, either lacking suitably located medical care or, if available, the ability to pay for it.[4] They included 24% of the poor, 33% of the unemployed, 6.2% of the elderly and 15% of black and 20% of hispanic adults. Despite diminished access to health care, many of these persons follow a life-style and have personal habits at least as healthy as most of the population. However, this group also includes disproportionately large numbers of the impoverished and illiterate whose circumstances preclude hearing about or understanding the significance of risk factors and whose dietary imperative may be finding money for the next meal rather than subtleties of proper nutritional balance. In this respect, urban minorities continue to be among the most disadvantaged in the Western world.

Growing up free from want in mostly white, middle-class, American suburbia provides no guarantee that a person will acquire good personal health habits. But it certainly helps! From the cradle to old age, minority populations have a higher morbidity and mortality for most diseases strongly influenced by preventive health measures and life-style. A growing national economy, commitment to desegregation and affirmative action, socially progressive income-support programs and the provision of improved medical services have contributed substantially over the past two decades to narrow the gap between the health states of blacks and whites, but a considerable disparity still remains. For example, the National Center for Health Statistics reports that, while postneonatal deaths for both blacks and whites declined steadily between 1962 and 1978, and rates for blacks fell more sharply than those for whites, the mortality risk for black children aged four weeks to one year is still more than twice that of their white counterparts.[5] During this same time span, neonatal mortality rates also declined for both blacks and whites, but the relative risk for black infants, compared with white infants, actually increased from 1.6 in 1962 to 1.8 in 1978. The Center points out that neonatal mortality is mostly related to birth weight and distribution and levels of neonatal care. Postneonatal mortality is thought to be determined by a combination of environmental forces, including socioeconomic conditions, demographic factors—that is, maternal age and parity—and the availability and use of health care. Poor and minority populations fare worse than average on nearly every one of these pertinent variables.

Should black infants born into poverty (and almost half of black children are still poor) survive unscathed the first year, they grow and develop lifelong health habits under unfavorable circumstances. They are most likely reared in a single-parent household, often with no adult at home during working hours. They live in inner-city, high-crime areas where increased rates of violence, alcoholism and drug abuse are everyday parts of life. They likely attend substandard schools and are often taught by ill-prepared, overworked, harassed and frightened teachers. They learn that survival is the major goal and, for boys, that prowess on the athletic field is often a more effective way to break out of the ghetto than is intellectual accomplishment. Teenaged and young adult men will find that they may have only one chance in two of acquiring a job. If the youngster born to economic deprivation is a girl, she is more likely than her middle-class counterpart to become an unwed, teenaged mother, untrained and unable to support herself in modern society. Moreover, she may be forced to seek public assistance, perpetuating what has come to be called "the permanent underclass." And despite two decades of steady progress, poor minority children are still less likely than their middle-class counterparts to obtain proper immunizations, receive care for acute illnesses, be taught good health habits and have remediable health problems corrected. Indeed, according to Rogers, poor children in America see physicians 23% less often than those from middle- or high-income families.[6]

The health consequences of socioeconomic deprivation, already evident in childhood and youth, continue to be manifest throughout adult life in statistics showing that in urban minorities there is an excess mortality from cardiovascular diseases, lung cancer, alcoholism and traumatic injury. Moreover, their already compromised health status suffers disproportionately from cyclical declines in the economy. Although indications are that bad economic times are associated with an overall increase in the nation's health problems, the highest risk of recession-connected illness appears to affect those who are in the lowest socioeconomic classes ("Health and the Economy [Editorial]," *Los Angeles Times,* July 5, 1984, p 4). This is hardly surprising, of course, because such groups traditionally have the greatest increases in unemployment and financial hardship during economic declines and, it is postulated, such stresses are linked to subsequent physical and mental illness.

Most likely, teaching prudent rules of health behavior relating to diet, weight control, smoking, alcohol and exercise will have minimal impact on the most unfortunate and impoverished segment of our population. Here, rather, we must redouble our efforts to improve the inner-city schools, increase employment opportunities, reinforce civil rights, develop accessible health services and raise the economic level for poor and minorities.

Nutrition

Taste for foods, particularly salty or sweet products, is usually acquired early in life, and good nutritional habits are believed to be an important element in personal health maintenance. Consequently, it is disconcerting to see poor children on their way to school munching a breakfast of potato or corn chips or a candy bar, too often purchased at the neighborhood liquor store, which is conveniently open at that hour to serve the needs of "serious" drinkers. Both acquired tastes and economic means appear to influence food preferences among differing sociocultural groups in America and, by currently accepted standards, the poor and minorities consume a less healthy diet than middle- and upper-income white families. According to the Nationwide Food Consumption Survey,[7] residents of central cities eat more poultry, eggs, grain products, dark green vegetables, soft drinks, fruit drinks and ades but less milk, milk products, total vegetables and sugar than do dwellers in the suburbs or nonmetropolitan areas. When

the survey tabulated results for persons in the lowest income households (less than $6,000 per year), compared with the highest income households (more than $16,000 per year), the former were found to eat more poultry, eggs, legumes, nuts, seeds, total grain products, cereals, pastas, white potatoes and dark green vegetables but less total meat and total milk products and less sugar and sweets. In directly comparing the nutritional habits of blacks and whites, the survey reported that the two groups had similar total meat intake but that blacks eat more pork, poultry, frankfurters, sausages, luncheon meats and fish. Whites of all ages, but especially teenagers and young adults, consume more milk and milk products. Blacks eat more than twice as much cereal and pasta as do whites; black women, in particular, eat more baked products, especially bread, rolls and biscuits. Blacks eat more than three times as many dark green vegetables as do whites and more eggs and legumes. Whites eat more fruit and drink more coffee than do blacks, but the latter consume more soft drinks and ades.

Thus, by any of three comparisons, the diet of poor, minority and inner-city residents differs substantially from that of their white, middle-class, suburban counterparts. The degree to which such dietary variations contribute to observed differences in indices of disease has not yet been established.

Poor housing, crowding, inadequate nutrition, despair and the social stigma of the ghetto itself contribute importantly to preventable health problems in the United States. However, other sociocultural forces are evident that generate large health differentials unrelated to poverty, ghetto life or access to medical care. Religious groups that prohibit the use of alcohol or tobacco by their members provide the clearest examples. Fuchs has spotlighted this influence in a telling comparison of the levels of health in Utah and Nevada, contiguous Western states.[8] For example, infant mortality is about 40% higher and mortality for young and middle-aged adults is 40% to 50% higher in Nevada than in Utah. The two states are similar with respect to family income, schooling, degree of urbanization, climate and many other factors usually thought to contribute to such variations in mortality. Fuchs attributes the large differences in death rates to the contrasting life-styles of the residents of the two states—Utah, with its devout Mormons who do not smoke or drink and lead quiet, stable lives, and Nevada, where inhabitants drink and smoke freely and exhibit high indices of marital and geographic instability. The death rates from cirrhosis and respiratory tract cancer, many times higher in Nevada than in Utah, lend support to these conclusions. Analogous decreases in deaths from cancer in the Seventh Day Adventists, another religious group with strong family and community bonds, whose faithful shun alcohol and tobacco and follow diets largely devoid of meat, also support this view.[9,10]

The Automobile

For most of the present century, the automobile has been a powerful sociocultural force in American life. It influences how our cities grow and where our industries develop. It brings farmers closer to the metropolis, obviating the isolation of rural living. It opens new recreational opportunities for much of our population and enables persons from one state to visit and know many different regions of the country. The automobile, too, represents a distinctive form of self-expression. In choosing a car and how it is driven, much is said about how we perceive ourselves and how we wish to be perceived by others. After a house, the automobile is the single largest purchase for most families. The manufacture of automobiles is both a determinant and a mirror of the economic health of the country. Concomitantly, automobile accidents, which are mostly preventable, account for nearly half of the more than 100,000 trauma-related deaths in the United States each year.

As noted in a recent report of the Council of Scientific Affairs of the American Medical Association (AMA), victims of automobile accidents are not randomly distributed among populations any more than are victims of lung cancer or malaria.[11] Rather, those injured by motor vehicles may be described in terms of host characteristics and other key epidemiologic variables such as the agent, environment, time of day and season. For example, it is well known that fatality rates per passenger mile are highest for men ages 16 to 29 years, a fact reflected appropriately in prevailing auto insurance premiums. Automobile design and road conditions, particularly weather, are other important risk considerations. However, human errors appear to account for about two thirds of motor-vehicle crashes and include inaccurate perception, excessive speed, inattention and improper evasive actions. Importantly, it is estimated that alcohol may be a factor in nearly half of fatal auto accidents.

Our society is not defenseless against the carnage wrought by the automobile. Thus far, however, we have lacked the collective will to act decisively on the issues of passenger restraint systems, speed control and drunk-driving penalties. Lap belts, alone, are estimated to be 27% effective in preventing serious injury during automobile accidents, and the lap-and-shoulder harness, standard in all cars sold since the mid-1970s, is about 42% effective.[12] Only about 12% of people bother to wear seat belts at all, however, and of the 43,000 people killed in car crashes in 1983, fewer than 2% were wearing them. This is a shocking indictment of our ability to convince people to "buckle up" in the interest of preserving their own lives.

Lacking any other remedy and faced with such massive noncompliance with voluntary restraint systems, the Transportation Department has recently declared its intent to order automatic restraints unless mandatory seat-belt usage is widely adopted by the states. This action is long overdue. The sharp drop in fatal injuries from automobile accidents subsequent to setting a speed limit of 55 miles per hour during the oil crisis provides another example of how society can act to reduce needless deaths. If these gains are to be maintained, however, strong public support will be required both to pass the seat-belt legislation in the necessary number of states and to avoid progressive easing of enforcement of the speeding restrictions.

Clearly there is much need for more research into both human and mechanical causes of motor-vehicle accidents. At present, the government allocates about $1 billion annually for cancer research and $500 million for investigations of heart disease, but only about $12 million is allocated for the problems of traumatic injuries, which involve a loss to society of as many youthful years as do either of the other problems.[13] In this regard, it is most timely that the AMA Council on Scientific Affairs is now encouraging physicians to recognize

the importance of motor-vehicle injuries as a priority health matter. Last year, the Council recommended a 12-point-action program that includes enhanced patient education, support for tougher drunk-driving laws and encouragement of national and federal organizations, such as the National Institutes of Health, the National Highway Transportation Agency and appropriate private groups, to devote more of their resources to research concerning vehicle-related injuries and their prevention.

The Media

Health-related information, including discussion of risk factors, nutritional facts and fads and statistics on excess deaths from alcohol and tobacco abuse, is widely disseminated in the media. Moreover, the importance of individual responsibility for health maintenance has been emphasized repeatedly in recent years by discussion of life-style questions in news articles, on radio and in television special events programs and talk shows. By and large, such reports on health topics are accurate, objective, clearly written and timely—new findings often reach patients even before physicians receive the medical journal in which they are published. Perhaps in response to the high degree of coverage, much of the public exhibits a strong interest in health matters, though they are often puzzled by prolonged debates over the safety of sugar substitutes, whether sodium is good or bad for hypertension and the merits of medical versus surgical therapy for coronary artery disease. Clearly, the media have become a powerful vehicle for health education.

However, the cultural influence of the media in shaping conceptions about health and in affecting health-related behaviors is much more pervasive than might be evident from examination of its various explicit health messages. Advertisements for snack foods, alcohol and tobacco products, for example, obviously encourage less desirable health habits. For television, our most important news and entertainment vehicle, it is much too often a case of "what you do speaks so loudly I cannot hear what you say."

Americans now spend more time watching television than doing anything else except sleeping and, according to a ten-year analysis carried out by Gerbner and co-workers at the University of Pennsylvania, the overall impact of such viewing upon health appears to be negative.[14] During prime-time dramatic programs, for instance, references to food and drink occur an average of nine times per hour. Grabbing a snack is nearly as frequent as eating regular meals and, in children's programs, snacks are nearly twice as frequent. Food advertising accounts for more than a quarter of prime-time and weekend daytime commercials but nearly half of these are for sweets, snacks and nonnutritious ("junk") foods.

Despite much violence on television, death from highway accidents is rarely portrayed and seat belts are hardly ever used except in commercials and then less than 25% of the time. While smoking is now more limited on television, drinking alcohol by both male and female characters is exceedingly common: from 1½ to 6 episodes of drinking are seen per program hour during prime time and in the daytime serials. Notably, whereas some 36% of prime-time major characters drink regularly, only about 1% are portrayed as having a drinking problem or alcoholism.

In assessing the data from their ten-year study, Gerbner and colleagues conclude that heavy viewers of television are more likely to be complacent about eating, drinking and exercise than those who watch less frequently. Hard-core viewers are also influenced by a dominant dramatic portrayal of physicians as able to solve nearly any medical problem, often against great odds. Hence, television programs tend to encourage a "live-for-today" attitude wherein persons deny responsibility for good personal health habits, presuming the "doctor can fix it" if something goes wrong. These attitudes are, perhaps, particularly devastating among the poorly educated and lower income groups who tend to watch television the most, who started with the poorest opportunities for health and who most need adequate health information.

Focusing on the influence of commercials in stimulating alcohol usage, a number of national organizations, including the Consumer Federation of America, the National Congress of Parents and Teachers, the National Parent Teacher Association and the National Council on Alcoholism, have recently banded together to launch a petition drive seeking either an end to alcohol advertising on radio and television or equal time for health messages (S. Farnsworth, "Drive to End Radio, TV Alcohol Ads Begins," *Los Angeles Times*, June 26, 1984, p 4). The new campaign, called SMART (Stop Marketing Alcoholism on Radio and Television), maintains that beer and wine companies spent $550 million on television ads last year and $135 million on radio time. In contrast, only $7.1 million in free time was allotted for alcohol public service broadcast announcements. The sponsors of SMART argue that the continuous flow of ads glorifying beer and wine consumption, viewed year in and year out, convey to young people the message that these beverages are essential for a happy, friend-filled and successful adult life and, hence, contribute to the frequency of alcohol abuse. The campaign has a goal of collecting a million signatures to pressure the President and Congress to adopt either an advertising ban or to increase anti-alcohol abuse broadcasts. While predictably the initial response of the alcohol industry to the campaign has been negative, it is more praiseworthy that the Distilled Spirits Council, representing the "hard liquor" producers, has since 1936 abided by a voluntary ban on broadcast advertising.

It seems likely that programmatic and commercial media messages, at least those on television, now largely negate the behavioral benefits that accrue from the time allotted to informative reporting and the discussion of health issues, though there are firm indications that well-planned and executed media campaigns designed to alter personal habits favorably can be quite effective. For example, the Stanford Heart Disease Three Community Program found that an intensive mass media health education effort over a two-year period substantially reduced cardiovascular risk factors among persons in the target communities compared with a control town.[15] Such an educational campaign gained added impact from the addition of face-to-face counseling provided to higher risk groups. A similar study carried out in Finland showed that a carefully orchestrated media campaign, closely linked to an array of community health education programs, successfully enabled the target population to reduce cardiac risk factors over a four-year period.[16]

Not all such attempts to use the media to change health

habits have proved effective.[17] Moreover, much remains to be learned about the choice of media, the most efficacious message content and the best reinforcement techniques. Undoubtedly the press, radio, news magazines and television could constitute valuable allies in the effort to promote better personal health habits; recruiting them for this purpose should be a major national goal.

Industry

Historically, American industry has been slow to react to the steadily mounting expense for the health care services that it purchases. For many decades, business restricted its health-related activities to occupational health and safety, executive medical examinations and employee health insurance premiums. Soaring costs, however, and their increasing impact on profit margins are now changing corporate involvement in matters of medical care. This involvement likely will continue to grow until the delivery and financing of such care become more manageable.[18]

An immediate and positive manifestation of this newfound corporate interest in employee health is a burgeoning of business-sponsored programs of health risk appraisal and risk reduction. Such programs, designed to reduce the prevalence of avoidable chronic illness, received a boost from recommendations of a 1977 Labor-Management Health Care task force, composed of major industry and union executives under the leadership of John Dunlap, former Secretary of Labor.[19] The task force came out strongly for greater business emphasis on health education for employees and their families and for considering new policies and programs that would provide exercise facilities, smoking cessation clinics and healthier foods in employee cafeterias and vending machines. Added impetus for such programs has come from Blue Cross and other insurance companies, particularly the Health Insurance Association of America. As a consequence, many companies have added stress-reducing and weight control efforts to their previously successful hypertension screening and alcohol programs, with related activities such as counseling for major crises (the death of a child or spouse, or divorce). An increasing number of corporations now offer their fitness-exercise programs in company gymnasiums and on company jogging trails.

The incentives to invest in risk reduction are impressive. According to O'Donnell and Ainsworth,[20] employers now spend an average of $1,200 to $2,000 per employee per year on medical benefits. Moreover, during the past decade, sick leave, disability and ancillary benefits have steadily become more generous under the terms of union contracts, adding to the magnitude of corporate benefit packages. As a consequence, medical care has overtaken pensions to become the largest benefit costs incurred by companies.

The payoff to business from implementing programs to achieve healthier life-styles appears to be worth the trouble and expense. Experience to date suggests that such programs raise productivity and reduce absenteeism. For example, during the first year at 130 General Motors plants, such programs were credited with a 50% cut in grievances, a 50% drop in accidents, a 40% decrease in lost time and a 60% decline in sickness and accident payments. Kennecott Copper credits its exercise program with a 55% reduction in medical care costs. Benefits from smoking cessation have been estimated at up to $600 per worker per year, and New York Telephone says that its program to encourage employees to give up smoking saves more than $2 million per year in absenteeism and medical costs.

To date, the evaluation of work-site risk-reduction programs has been spotty, and the effectiveness of differing approaches must be assessed more thoroughly. However, the Washington Business Group on Health, an influential affiliate of the Business Round Table, and a number of large corporations are supporting the development of health evaluation tools as part of their growing examination of means to better control increased health care costs.

Fashion

By its nature, fashion is subject to change without notice, usually for reasons that defy rational explanation. Whatever its murky genesis and dynamics, however, fashion is a potent influence on individual behavior and, when it works to reinforce good health habits, merits praise and encouragement. Such is the happy case when, as in recent years, fashion setters have dictated that healthier life-styles are desirable and have prompted a large segment of the population to take up regular exercise and decrease caloric intake. While excessive jogging or aerobic dancing and imprudent "fad" diets have harmed a few, the growing acceptance of good health habits as "fashionable" is an enormous overall plus and greatly enhances organized professional efforts directed at risk reduction and personal health maintenance.

It would be nice to believe that physicians could set fashion trends in matters of health. Obviously physicians can and do play an important role in pointing the right direction. When it comes to capturing the public's interest and action, however, Jane Fonda may prove to be a more effective force than our most comprehensive health education programs. We need more such allies.

Conclusion

It is abundantly clear that physicians need to do a better job of informing the public about established health risks and to develop more effective methods to encourage personal health maintenance. To achieve these objectives, we must also recognize and more successfully neutralize the counterforces in society that influence health behavior negatively. The most readily accessible are the powerful tobacco and alcohol industries, which encourage use of their products directly through massive advertising campaigns and obtain indirect support from the media, at least on television, through frequent portrayal of product use in ordinary programming. More vigorous public education programs on the hazards of alcohol and tobacco, severe restrictions on their advertising and a pronounced increase in taxes on consumption of both products would do much for the health of our citizens with little sacrifice of individual rights.

The national media could be physicians' closest ally in improving the nation's health. The media should receive strong encouragement including financial incentives and, if necessary, additional regulatory guidance to examine more critically the health impact of their programming and advertising and to make necessary adjustments. Freedom of the press entails an overall obligation to act in the public interest.

Industry should be further encouraged to extend work-site

programs in health maintenance and risk reduction. "Bottom-line" improvements should be a sufficient incentive, and the results to date should be widely circulated.

Of greatest importance, physicians must better reach and assist the lowest socioeconomic segment of the population whose opportunity to learn about and assume greater personal responsibility for their own health is still compromised by the setting into which thay are born and raised. It is unfortunate that some, who feel that the maximum proportion of the nation's wealth that should be spent on "social" programs has been reached, cynically propound the need for greater individual responsibility in lieu of attacking unsolved societal ills. It would be tragic if current efforts to reduce health risks and encourage healthier life-styles were to serve as an excuse to renege on our earlier national commitment of equal access to medical care services and equal opportunity in life for all our citizens.

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Understanding Genetic and Environmental Risk Factors in Susceptible Persons

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Most major chronic diseases probably result from environmental factors accumulating over time in genetically susceptible persons. A detailed family history assessment can help identify the subset of the general population with a strong predisposition to certain major diseases. An understanding of the environmental factors promoting disease development will facilitate more effective prevention or delay disease in a targeted susceptible population. To effectively use this growing knowledge in genetics and epidemiology, health professionals need to motivate people to follow sound recommendations for preventing and delaying disease.

To increase the efficiency and effectiveness of strategies for health promotion and disease prevention, family history data can help determine those diseases for which persons have the greatest risk: They can then concentrate their primary efforts on those preventive measures that will most likely benefit them.

(Williams RR: Understanding genetic and environmental risk factors in susceptible persons, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:799-806)

What determines which diseases will most likely develop in a person? Is there a way to predict which few specific illnesses should be of greatest concern to a given healthy person? Realistically, will many persons effectively comply with all of the well-publicized recommendations for detecting early or preventing numerous common diseases? Can physicians help target a few screening and preventive measures of greatest value to specific persons? An understanding of the genetic and environmental determinants of disease can provide a solid rationale for more effective prevention, earlier detection and more specific and more effective treatment of disease. The following are the practical steps required to accomplish these goals.

Genes Plus Environment Equals Disease

Many common diseases seem to occur among genetically susceptible persons who have been exposed to the appropriate environmental factors. Age also plays an important role in the development of most diseases, but age probably represents the accumulated effects of both genetic and environmental factors over time. Many diseases also show different rates of occurrence according to sex. This probably represents either environmental or inherited differences between men and women. While some diseases appear to occur on a totally chance or unpredictable basis, the actual role of chance or random events seems to diminish considerably as more information is uncovered about the pathophysiologic mechanisms.

Several major types of environmental factors are listed in Table 1. Some of the first and most dramatic discoveries in preventive medicine came from infectious disease epidemiology. Application of that knowledge has led to the eradication or control of illnesses such as smallpox, polio, typhoid fever and tuberculosis, which were previously the most common causes of morbidity and mortality. Current epidemiologic studies focus on the causes of major chronic diseases. Early successes are already suggested by decreasing death rates for stroke and coronary diseases in the United States.[1] Studies of general populations and control subjects in clinical trials report improving profiles for major risk factors such as cigarette smoking,[2] hypertension[3] and hypercholesterolemia.[4] One would hope that continued application of expanding knowledge of environmental factors listed in Table 1 could lead to eradicating and controlling the chronic diseases that are currently the major health problems in well-developed countries of the world.

Some of the environmental factors listed in Table 1 aggregate strongly in families, accounting for some of the familial disease aggregation. Thus, the detection of smoking-related diseases within a family may help target a family with "a smoking tradition" that needs to be broken with a conscien-

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tious and cooperative effort of health professionals and family members.

Different types of genetic factors affecting disease occurrence are described in Table 2. Perhaps the genetic effects most easily understood are those following simple Mendelian inheritance. When biochemical or chromosomal markers have been discovered to trace the gene carriers, it can be shown that in some cases the genes are "highly penetrant," with a large percentage of persons who carry the gene also expressing the disease, such as men who have familial hypercholesterolemia. In other cases, genes have been found to have "low penetrance," with most of the gene carriers not expressing the disease, such as those who have insulin-dependent (type I) diabetes mellitus. One of the main goals of current research is to identify gene markers for specific inherited diseases and then identify the environmental and life-style differences between gene carriers who do and do not express the disease. Future prevention strategies will use this knowledge to prevent disease occurrence in known gene carriers detected soon enough to modify their environmental exposures.

Probably most physiologic traits and many diseases represent the blending of the effects of many different genes, so-called polygenic traits. There is often an additional blending of environmental factors leading to a truly multifactorial etiology. In addition, there is often a mixture of both major gene and polygenic effects in the population. As an example, serum cholesterol level is a polygenic trait in the general population, with a small but important percent of persons exhibiting major gene effects with very high serum cholesterol levels and a risk for early heart attack. In addition, there are environmental factors that can have substantial effects on a person's serum cholesterol level regardless of their major gene or polygenic determinants of serum cholesterol.

A person's integrated risk of disease will represent the summation of genetic predisposition from major genes and polygenes, interacting with specific environmental factors whose strength and duration of exposure combine to produce a person's individual disease risk.

Some diseases may involve a large number of genetic and environmental factors.[5] While many of the details are still being identified by research studies, simple intuition can help us to see these principles in operation. In most heavy cigarette smokers, lung cancer does *not* develop. They must be persons who either lack genetic susceptibility or possibly even have genetically determined resistance to the well-documented carcinogenic effects of cigarette smoking. Figure 1 shows lung

TABLE 1.—*Environmental Factors Affecting Disease Occurrence*

Biologic and Immunologic
Bacteria
Viruses
Fungi
Protozoa
Insect and animal vectors
Allergens
Personal Habits and Life-style
Smoking
Physical exercise
Dietary intake
Chemical Exposures
Toxins
Pollutants
Medication
Solvents, fumes
Contaminants
Physical Environment
Climate
Radiation (ultraviolet, gamma and x-ray)
Physical trauma
Social/Psychological Milieu
Marital and family status
Occupational satisfaction and stress
Learned skills and coping capacity
Shared Environment in Groups
Families (spouse, siblings)
Geographic locations (sun exposure, altitude)
Ethnic and racial groups (diet customs)
Religious groups (health codes, sex taboos)
Individual communities (water supply)
Countries (food-processing systems)

TABLE 2.—*Types of Genetic Factors Affecting Disease Occurrence*

Major Genes (one or two loci, few alleles)
Dominant, recessive or additive?
Gene frequency high or low?
Autosomal or sex-linked?
Totally penetrant?
Partially penetrant?
Factors affecting penetrance (age, sex, environmental factors, other genes, chance)?
Polygenes (many loci and/or alleles)
Blending of effects, none predominate or stand out
Often blending with environmental factors (multifactorial)
Mixture of Major Genes and Polygenes
Noticeable effect of major gene (same characteristics as above)
Background variation around each major gene phenotype due to polygenes

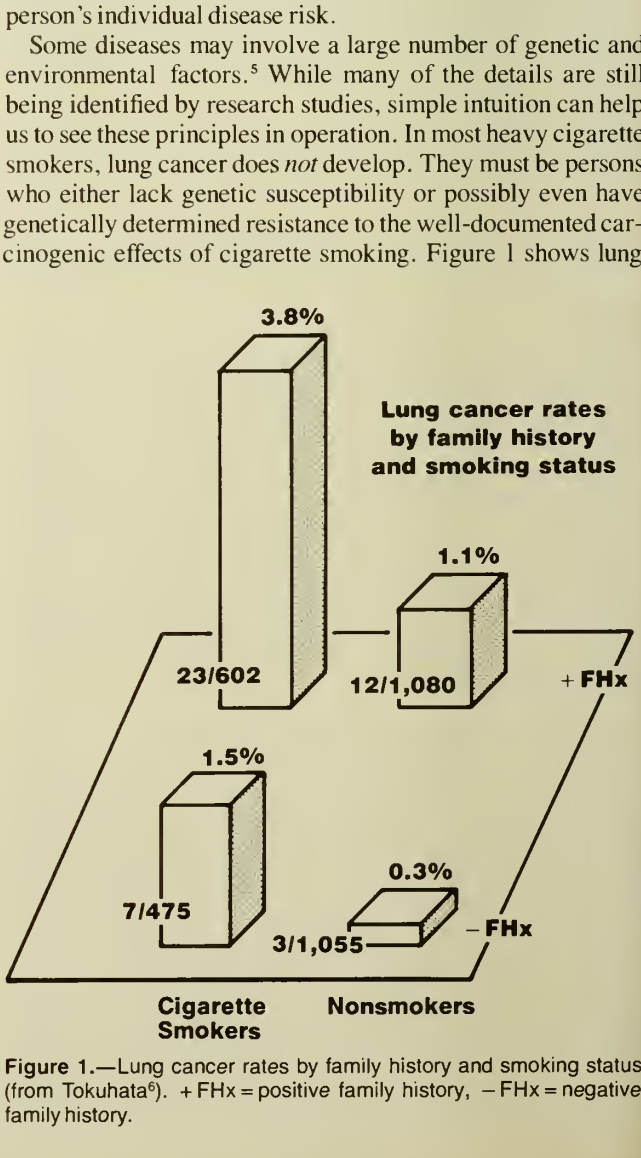

Figure 1.—Lung cancer rates by family history and smoking status (from Tokuhata[6]). + FHx = positive family history, – FHx = negative family history.

cancer rates reported for smokers and nonsmokers with and without first-degree relatives who have lung cancer. Whereas smoking and familial predisposition each seem important, their combined effects are most dramatic.

Past studies of Japanese men have shown rates of early coronary heart disease less than a fourth those observed in young men in the United States.[7] Initially one might have suspected that these differences were due to genetic factors. However, a study of Japanese men living in Japan, Hawaii and California showed parallel increases in serum cholesterol levels and early coronary heart disease rates.[8] Both were lowest in Japan, intermediate in Hawaii and highest among Japanese men living in California. This suggests that among genetically similar persons, significant changes in environmental exposures have dramatic effects on disease occurrence.

Diseases With Genetic Predisposition

Hundreds of well-defined major gene syndromes leading to rare genetic diseases have been described.[9] Methods for screening and genetic counseling are well developed and often efficiently applied for some of these rare disorders. The main emphasis of this report is to concentrate on the possible benefit that can be gained from increased awareness of genetic predisposition to *common* chronic diseases encountered often by practicing physicians. Some of these common chronic diseases are summarized in Table 3. Perhaps the most striking example is early coronary heart disease. Several approaches indicate that a very strong family predisposition to early coronary heart disease occurs in about 5% of the families of the general population, and yet these coronary-prone families account for more than 50% of cases of coronary disease occurring before age 55.[10-12] In about a fourth of these families, a single serum cholesterol test may identify greatly elevated levels as the major inherited causal factor.[10] While coronary disease usually develops by age 45 in men who have familial hypercholesterolemia, there is evidence that men who carry this gene could be protected by healthy environmental factors. Pedigree analyses of great-grandfathers of current hypercholesterolemic coronary victims found definite gene carriers living in the 1800s who survived into their 60s, 70s and 80s (R. R. Williams, MD, and colleagues, unpublished data, December 1984). Developing data from clinical trials also support the feasibility of lowering coronary risk through the treatment of hypercholesterolemia.[13,14]

Preliminary data suggest that 34% of high-risk families have cigarette smoking as the only known concordant risk factor among brothers with coronary disease in their 30s and 40s.[10] Thus, in some persons, avoiding or stopping smoking may totally eliminate a very high risk for premature coronary disease. Results of this study of high-risk coronary families also suggested a magnified detrimental effect of cigarette smoking among coronary-prone men regardless of their underlying risk factor.[10] Multifactorial risk reduction may have its greatest practical benefit in high-risk families.

Hypertension also seems to play a significant role in about a fourth of coronary-prone families. Methods for early detection and treatment of hypertension are already well developed and practiced by many physicians. If these efforts are concentrated in high-risk families, the benefits could be substantial.

Opportunities for early detection and risk factor modification for the prevention of other strongly familial diseases are suggested by the list in Table 3. A detailed discussion of each of these disorders individually is beyond the scope of this review. Just to reinforce the potential for *current* practical application of intervention in high-risk families, a few other examples will be cited. Cancers of the breast, colon and lung are the most common and the most familial.[15]

In a study of 1,000 population-based breast cancer deaths in Utah a third of the patients had sisters with breast cancer, suggesting a strong familial tendency (Mark Skolnick, PhD, unpublished data, August 1980). Preliminary reports already suggest possible chromosomal markers to identify persons carrying this genetic predisposition.[16] Table 3 lists several reported environmental risk factors for breast cancer.[17-21] It is possible that genetically predisposed persons have a multiplicative risk from exposure to these variables and could benefit from their removal. Even if control of environmental risk factors does not completely eliminate the familial risk of breast cancer, applying effective screening procedures (breast self-examination, physician screening, mammography and the like) can lead to the early detection and surgical cure of breast cancer in many of these women.

Colon cancer is also strongly familial in certain persons. Some knowledgeable gastroenterologists working with high-risk families strongly feel that careful screening of high-risk persons can result in early detection of colonic polyps before cancer has developed or spread and effectively eliminate the risk of metastatic colon cancer in most persons with strong predispositions.[22]

The combined contributions of genes and environment to lung cancer are dramatically shown in Figure 1. From this illustration it is self-evident that avoiding cigarette smoking is an important preventive measure for persons who have relatives with lung cancer.

The application of this preventive strategy is not limited to common and prominent diseases such as cancer and coronary heart disease. While they are less common and perhaps less well appreciated, disorders such as hemochromatosis should also be targeted for preventive strategies. In the past, this disorder has often gone undiagnosed. Accumulating iron stores in heart tissue or pancreas have led to heart failure or diabetes mellitus. Unsuspecting physicians have provided only symptomatic treatment, with eventual early death of patients. Screening tests can now be used among close relatives of patients known to have hemochromatosis to identify those carrying the disorder.[23] Frequent phlebotomy is an effective treatment that should eventually produce a normal life span in persons carrying this disorder.

What Can Be Learned From a Thorough Family History

A thorough family history can help answer questions like these: Did a genetic predisposition play an important role in this person's early heart attack? Do close relatives need screening or further follow-up? How strong is this family disease tendency? Does it affect men and women the same? What is the usual age among family members at onset of disease? Before what age should screening and preventive measures be instituted? Which risk factors have been present in affected family members? What is the pathophysiologic mechanism leading to the disease? What specific suggestions

TABLE 3.—*Chronic Diseases Thought to Have Genetic Predispositions*

Disease	*Pathophysiology (or Hypotheses)*	*Genetic Details*	*Environmental Factors*
Coronary heart disease (especially *early* disease)	Familial hypercholesterolemia		Dietary fat
	LDL receptor defects	Dominant	Saturated fat
	Other high cholesterol	?	Polyunsaturated
			Total fat intake
	Low HDL	?	Exercise, alcohol, diet
	Endothelial factors	?	
	Platelet factors	?	Smoking
	Apolipoproteins	?	?
	Diabetes I and II	See below	See below
	Hypertension (especially early onset)	See below	See below
	Multiplicative interactions of family history and risk factors		
Stroke	Hypertension and diabetes	See below	See below
Hypertension	Heterogeneous	Polygenic?	Salt, stress, obesity
	Age at onset	Major gene?	Polyunsaturated fat
	Severity? Cause?	Highly penetrant?	
Type I diabetes mellitus (insulin-dependent)	Islet cell destruction	Recessive?	Viral infection
	Immunologic cause	<50% penetrant	Seasonal variation
		HLA linkage and association on chromosome 6	Complications a function of blood sugar control for years
Type II diabetes mellitus (non-insulin-dependent)	Insulin resistance	80% to 100% penetrant	Obesity
	or	Dominant?	Dietary sugar and fiber
	Decreased production	RFLP association to insulin gene on chromosome 11	Exercise protective
			Complications a function of blood sugar control and function
Breast cancer	Estrogen-related	Some dominant	Age when first child born
	Certain benign tumor precursors	50% to 90% penetrant in some families	Obesity
			Dietary fat
			Alcohol use
			Female hormones
Colon cancer	Several different types of syndromes	Some dominant	Fiber intake
	Often benign polyps are precursors		Dietary fat (converted by bacteria to carcinogens)
Lung cancer	Chemical carcinogens from environment encounter enzymatically susceptible subjects	Known familial aggregation ± smoking	Cigarette smoke
			Environmental pollutants
			Radiation exposure
Rheumatic heart disease	Immunologic cross-reactivity to bacteria and heart valves	Familial aggregation	Group A β-streptococcal bacterial infection
Asthma and other allergies	Immunologically reactive	Familial aggregation	Many possible allergens—fur, dust, pollen, mold, etc.
			Avoidance to prevent
Autoimmune disorders	Autoantibodies to thyroid, adrenal, synovium, platelets	HLA-linked on chromosome 6	Viral infections trigger immune responses
Rheumatoid arthritis			
Hashimoto's thyroiditis and Graves' disease			
Addison's disease			
Idiopathic thrombocytopenic purpura			
Type I diabetes mellitus			
Systemic lupus erythematosus			
Psychiatric disorders			
Manic-depressive	Neurochemical disorders in brain tissue	Strongly familial and likely genetic in twin, adoption and family studies	Uncertain influence
Depression			Several dramatic drug therapies for manic-depression and depression
Schizophrenia			
Kidney stones	Mineral-acid-base imbalance	Very familial	Milk?
			Soda pop?
			Other fluids?
Gallstones	Fat, cholesterol, bilirubin balance	Quite familial	Dietary fat
			Obesity?

ATPase=adenosine triphosphatase, G6PD= glucose-6-phosphate dehydrogenase, HDL=high-density lipoprotein, HLA=human leukocyte antigen, LDL=low-density lipoprotein, RFLP=restriction fragment-length polymorphism

Disease	*Pathophysiology (or Hypotheses)*	*Genetic Details*	*Environmental Factors*
Obesity (probably very heterogeneous)	Less energy wasted? ↓ Thermogenesis in brown fat? Other basic energy differences like ATPase pumps? "Thrifty gene"?	Major genes in animals Clusters in families Assortative mating Monozygotic twin similarity > dizygotic Racial group (American Indians and Polynesians)	Dietary fat, sugar and total calories Stress, etc. affecting appetite Exercise level Cultural perceptions (attractive to be fat or thin?)
Gout	Several different enzyme defects found	Several autosomal major genes	Dietary intake of meat and the like
Multiple sclerosis	Autoimmune demyelination of nerve fibers	HLA association Poorly penetrant Monozygotic twins often discordant	Slow virus? Climate-dependent
Peptic ulcer disease	Excess acid production and/or decreased mucosal resistance	Biochemical markers of affected subjects Variable penetrance	Stress Diet Dramatic drug therapy
Hemolytic anemia	G6PD deficiency Red cell hemolysis precipitated by exposure to drugs or infections	X-linked recessive	Aspirin Antibiotics Infections
Lactose intolerance	Deficiency of lactase enzyme in intestinal mucosa	Very common in blacks	Milk products
Alcoholism	Associated with other psychiatric disorders Possible neurochemical origin?	Familial (due to genes and/or family environment?)	Ethyl alcohol intake Social factors
Hemochromatosis	Increased iron absorption	Linked to HLA on chromosome 6 Recessive Penetrant	Treat with phlebotomy and prevent organ damage from iron loading

ATPase=adenosine triphosphatase, G6PD= glucose-6-phosphate dehydrogenase, HDL=high-density lipoprotein, HLA=human leukocyte antigen, LDL=low-density lipoprotein, RFLP=restriction fragment-length polymorphism

could be given for disease prevention, screening and treatment?

Current research is concentrating on identifying specific syndromes and separating out the heterogeneity of many common chronic diseases such as diabetes mellitus, coronary disease, hypertension and cancer. Family history information will be increasingly useful in helping to identify these specific syndromes. This improved understanding of pathophysiology will lead to better prevention, screening and treatment.

How to Obtain a Good Medical Family History

The usual *brief screening family history* taken by a physician during a workup should include three questions. First, does the person know of any medical problems that tend to run in the family? Next, have any close relatives (parents, grandparents, siblings, aunts, uncles or offspring) had premature (before age 55) heart disease, cancer, diabetes mellitus, high blood pressure, stroke, bleeding disorders, emotional illness, serious problems with allergies or neuromuscular problems? Third, what was the age of onset and treatment for any relatives reported to have the disease? Even such a brief family history will often flag striking family problems that deserve further attention.

A *detailed family history* should be obtained when a brief family history suggests a possible disease tendency. It begins with enumerating all first- and second-degree relatives (see Figure 2). List at least first names to facilitate further questions and accurate communication. For each person, list vital status, age (now or at death) and cause of death. For specific targeted diseases that seem to occur in the family, the age of onset should be recorded for each family member with the disease. This is especially important for common diseases such as high blood pressure, diabetes mellitus and coronary heart disease in which an early age at onset would indicate a strong family history whereas a later age at onset may not be a flag of a positive family history at all. The number of spouses and children of each person and their current location or location at death can be useful as a springboard for further information gathering, screening and preventive measures.

To decrease the expense of family history screening, self-administered questionnaires have been developed and piloted among families of 12,000 high school students in Texas and Utah.[24] Self-administered questionnaires filled out by families in their own home have the advantage of allowing them to contact relatives to obtain information or to even review their own medical records or prescriptions while filling out the forms. Probably the best accuracy can be obtained from a combination of self-completed questionnaires subsequently reviewed by a physician or a nurse.

If a positive family history is indicated, further verification is often worthwhile before initiating extensive measures of screening and prevention in family members. For those relatives indicated to have specific diseases and risk factors, contacting these relatives to obtain the details of their medical problems and copies of the medical records can help distinguish about 10% to 30% of false-positives that may be reported in many family histories. Heart operations for rheumatic valvular heart disease will often be confused with coronary disease; benign growths may be confused with cancer and so forth. Only detailed medical records will help distinguish some of these confusing situations.

The fourth and final level of family history evaluation is the

MEDICAL FAMILY HISTORY QUESTIONNAIRE

Date _____ ID # _____

Address _____ Phone _____

_____

	A FIRST NAME	B MIDDLE NAME	C MAIDEN NAME	D LAST NAME(S)	E Number of MARRIAGES	F Number of CHILDREN	G Month & Year of BIRTH	H Month & Year of DEATH	I STATE (Now or at Death)	J BLOOD RELATIVE (+/−)	K LIVING OR DEAD (L/D)	L AGE (Now or at Death)	M SEX (M/F)	N RACE (W. B. H. I. A. X)	D SMOKES CIGARETTES (0 ½ 1 2 (C or F)	P DRINKS (− + ++) ALCOHOL	D-1 WEIGHT (S. A. M. V. E)	D-2 WEIGHT OF SPOUSE (S. A. M. V. E)	D-3 NUMBER OF OVERWEIGHT OFFSPRING	LIST AGE AT ONSET: R STROKE (Hospitalized or Died)	S HIGH BLOOD PRESSURE (On Treatment)	T DIABETES (On Treatment)	U HIGH BLOOD CHOLESTEROL	V HEART ATTACK (Hospitalized or Died)	W CORONARY BYPASS HEART OPERATION	X ANGINA CHEST PAINS (On Treatment)	Y OTHER HEART DISEASE (On Treatment) (See Code)	LIST AGE: Z BREAST CANCER	AA LUNG CANCER (Started in Lung)	BB COLON CANCER	CC OTHER CANCER (Write down 3 letter code from attached list)	DD OTHER SERIOUS ILLNESS	EE CAUSE OF DEATH
1 YOU																																	
2 Father																																	
3 Mother																																	
4 Bro/Sis																																	
5 Bro/Sis																																	
6 Bro/Sis																																	
7 Bro/Sis																																	
30 Spouse																																	
31 Son/Dau																																	
32 Son/Dau																																	
33 Son/Dau																																	
34 Son/Dau																																	
50 Paternal Grandfather																																	
51 Paternal Grandmother																																	
52 Aunt/Uncle																																	
53 Aunt/Uncle																																	
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76 Aunt/Uncle																																	

Figure 2.—A sample of a Medical Family History Questionnaire for targeting first- and second-degree relatives.

TABLE 4.—*Medical Family History*

When	*Why*
1. *Patient with disease* that might be familial Check family history	1. If positive family history, help close relatives avoid the same problem
2. Patient *might* have disease Check family history	2. Positive family history increases suspicion Special tests or monitoring may be justified
3. General screening tool Broad family history overview	3. Be alert to family tendencies Plan future screening procedures

How? (What data should be collected)

1. *Sex, age, vital status* for *all target relatives and spouse*
   1st-degree relatives: Parents, siblings, offspring
   2nd-degree relatives: Grandparents, aunts and uncles

2. *Diseases and cause of death* Age at diagnosis? Treatment given?	3. *Risk factors* Years of exposure? Modification and outcome?

What is learned from a detailed family history?

1. Is it familial?	6. Pathophysiology?
2. How strong a tendency?	7. Which relatives need help?
3. Affect men and women alike?	8. Age to start screening?
4. Usual age at onset?	9. Best way to prevent, screen or treat?
5. Which risk factors involved?	

detailed investigation of a pedigree, including *screening* of *family members* when a particular disease is sought. Among families with hypercholesterolemia, blood specimens should be obtained from first-degree relatives of known affected persons. Sequential screening should in turn be focused on the next set of first-degree relatives of the persons found affected in the screening process. Members of a family at high risk for colon polyps and cancer should receive special screening for occult fecal blood, polyps and the like.

Of these four levels of family history evaluation (brief screening, detailed family history, verification and pedigree investigation), all except the first require special preparation, a substantial investment of time in training persons for collecting and processing family history information and conscientious follow-up in collecting material. A thorough family history will not be free. On the other hand, where family tendencies would appear to be present, an investment of several hundred dollars for personnel time and forms is probably more helpful than many laboratory tests of equal or greater expense generally applied in medical evaluations.

Need for Sensitivity to Patients' Privacy and Feelings Regarding Their Family History

Will highlighting a person's positive family history induce stress or relieve it? Should a strongly positive family history always be brought to the attention of a person? If measures are available for screening, prevention and more effective management of the disease for persons aware of their positive family history, then the net benefits of family history assessment outweigh the possible detrimental effects. In many cases, such as significant early coronary disease or breast cancer, the family members are usually aware of their family tendency but are often not aware of measures that can be used for better detection and prevention. Experience with members of coronary-prone pedigrees indicates that, whereas most of them are generally aware of their disease tendency, few of them are really receiving maximal medical support and help in screening and prevention.

While collecting and sharing family history data, health professionals should carefully protect the privacy of the patient. Information should not be shared even with a patient's relatives without express permission and notification. Illegitimate children, multiple marriages and sensitive illnesses are all details that may be embarrassing to persons if shared with others, including some close relatives. Probably the best approach is to have each family member interested in a family history evaluation complete detailed family history forms. Completing these forms will require communication among family members, in which case they will be mutually sharing information that they feel is appropriate.

Genetic counseling approaches one of the most sensitive areas of medicine. Health professionals should help patients operate within their own personal beliefs and not force beliefs upon them. If there is any need to discuss issues such as family planning, prenatal diagnosis and abortion, these topics should be dealt with carefully. Health professionals should educate patients regarding their options, but allow them to make their own decisions.

Expected Developments in the Near Future

Technologic advances are rapidly producing tools for characterizing specific syndromes. This will allow efficient dissection of the heterogeneity of many common syndromes such as early coronary disease, obesity and hypertension. A better understanding of the steps leading to the disorders in specific persons will pave the way for more specific management tailored to the mechanism of a disease's occurrence.

Dramatic advances in identifying major gene effects should follow the rapid application of *genetic markers.* In the past, geneticists have used a variety of cell and tissue antigens and protein polymorphisms in an attempt to identify chromosomal linkage with major gene traits. The success of these efforts in the past has been hampered by the high expense of obtaining these marker studies, the inconvenience of diverse biologic samples required to cover available markers and, perhaps most important, the lack of a high degree of polymorphism required to produce useful information from many mating situations studied. With only two or three different forms of a marker, spouses often have identical haplotypes, making it impossible to detect disease associations in offspring and siblings.

Restriction fragment-length polymorphisms (RFLP) represent a recent dramatic breakthrough in gene marker strategies.[25] Under this new system variations in biochemical patterns of the DNA molecules themselves are examined. One single biologic specimen (DNA material from the nuclei of leukocytes from about 50 ml of ordinary venous blood) has the potential of providing polymorphic gene markers that can map major genes on virtually any chromosome in the body. Most geneticists familiar with this new technology project that within several years they will have discovered RFLP markers equally spaced across each chromosome of the body that will make it possible to map approximately 95% of major genes. The leukocyte specimens can be frozen for future use, and the prepared DNA material can be analyzed multiple times for different markers, allowing much more efficient use of the specimens taken from patients.

TABLE 5.—*Why the Gap in Applying Pathophysiology for Prevention?*

Needs	*Sample Shortfalls*
Educating health professionals	Some still think "You can't change genes, so you can't help someone with a positive family history"
Finding and screening high-risk persons and families	Diseased probands are treated without offering screening and risk reduction to their offspring
Targeted "full dose" education for high-risk persons	Shotgun low-dose publicity does not get enough information to the small percentage who need it most
Better follow-up of screening results	"When they screened me, they said I was high, but I never have been treated"
Better follow-up for compliance with medication	"I stopped taking the medicine because I didn't feel any better"
Effective incentives for needed life-style modification	"I stopped smoking a dozen times"

If the entire effort in gene markers is concentrated on this single methodology, one would expect improving efficiency and increasing cost-effectiveness, enabling future screening efforts to identify gene carriers in families with known major gene disease predispositions.

Once markers are generally available, then known gene carriers can be studied for other factors to identify exactly which environmental factors affect a given gene's expression. The net result will be a detailed definition of the step-by-step processes in the pathogenesis of these major diseases. Examples are already available in illnesses such as type I diabetes mellitus and low-density-lipoprotein-receptor defects in familial hypercholesterolemia. This level of understanding for other major genetic syndromes will provide unprecedented opportunities for disease prevention, amelioration and targeted treatment.

Because these dramatic technologic advances are considered to be a near certainty by many experts, the real challenge of the future appears to be the behavioral and social issues highlighted in Table 5. Once disease prevention is understood, the question is, can we motivate patients to follow sound advice?

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Maternal and Fetal Well-being

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Pregnancy outcomes can be improved by following modern recommendations for personal health maintenance. Adequate caloric intake, reflected by a weight gain of about 10 to 12.3 kg (22 to 27 lb) for women of average build, is associated with the lowest rate of perinatal mortality. Maternal dietary protein supplementation should generally be avoided because it may be associated with low-birth-weight pregnancies. Abstinence from social drugs offers the greatest positive opportunity to modify the health of a fetus. Serious perinatal infection can be prevented by preconception immunization (rubella), food hygiene (toxoplasmosis) and attention to the expression of virus in the mother (herpes simplex). Available data do not correlate exercise programs begun before pregnancy and continued during pregnancy with adverse fetal effects. Athletic capacity need not diminish postpartum. Most employment may safely continue until delivery. Routine recommendations for prolonged maternal disability leaves are not medically warranted.

(Shy KK, Brown ZA: Maternal and fetal well-being, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:807-815)

Americans are caught up in a new wave of health consciousness. The importance of personal health maintenance is enhanced during pregnancy by virtue of the responsibility for a new life. Frequently coupled with health consciousness is consumer awareness that does not allow physicians to rest on tired dogma in response to new, or old, questions. On a daily basis, patients are confronted with concerns about diet and nutrition, drug exposure, perinatal infectious risks and the advisability of exercise and employment during pregnancy. Pregnancy outcome can be influenced substantially by the patterns of response to these concerns.

Diet and Nutrition

Energy Requirements (Calories)

During the past two decades, follow-up studies and controlled trials of nutritional supplementation have better clarified the influence of caloric restriction on pregnancy outcome. Food shortages during World War II, because of their severity and abrupt onset and resolution, became in effect a natural experiment on severe dietary restriction.[1] A famine was induced by a Nazi embargo during the 1944-1945 winter in the western urban regions of Holland. The famine lasted six months. Overall, at the height of the famine, mean birth weights were reduced about 300 grams. Pregnant women exposed to the famine throughout their entire third trimester had infants of considerably lower birth weights, whereas those pregnant women exposed to famine only during the first 27 weeks had infants with little reduction in birth weight. Proper caloric support and nutrition returned immediately after the embargo was lifted. Follow-up studies of 125,000 men 19 years later did not show an alteration in the mental performance of children born during the famine.[2] Because of the severity of the famine, it is not possible to generalize the birth-weight effects of famine to contemporary diets, which may lack certain recommended vitamins and minerals[3] but otherwise provide sufficient caloric support.

Subsequent experimental[4,5] and nonexperimental[6] caloric supplementation trials have indicated a beneficial birth-weight effect only for the pregnancies of women who are in a negative energy balance or who are underweight and by inference underfed at the time of their pregnancy. Net caloric supplementation of about 425 calories per day beginning during the 16th week of pregnancy resulted in a mean birth-weight increase of 224 grams in Gambian women during the wet season, a period of food shortage and high work load. During the dry season, a period of ample food and positive energy balance, the tendency was for a *negative* effect of supplementation on birth weight.[5] A similar experimental trial of Asian mothers at the Sorrento Maternity Hospital in Birmingham, England, yielded the same results.[4]

North American studies indicate that the apparent adverse effect of dietary supplementation to adequately fed mothers is probably greatest when the caloric supplementation is given as protein.[6-8] In an experimental trial of high-protein dietary

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supplementation for low-income black women in New York City, the mean birth weight was decreased slightly with protein supplementation (40 grams of casein a day).[7] More important, and actually startling, was the significant excess of very premature births in the protein-supplement group (9%) versus the controls (5%).[7] Associated with the prematurity were increases in intrauterine growth retardation and neonatal mortality. The effect of the high-protein supplement was different for women who smoked. Birth weights of their infants were greater than for comparable smokers who did not receive protein supplementation. In the Sorrento study, birth weights were also lower among the adequately fed women who received high-protein caloric supplements. Moreover, nutritionally deprived rhesus monkeys given protein supplementation also have an excess of premature births[9]; as in the New York study,[7] the maternal weight gain produced by protein supplementation was not transmitted into birth weight.

Maternal Weight Gain

Measuring maternal weights throughout a pregnancy is a practical alternative to counting calories for estimating energy and nutrient availability to a fetus. Weight gain of a mother and her prepregnancy weight both have positive linear associations with the birth weight of her child.[10] On a theoretical basis, the expected maternal weight increment can be estimated from the physical alterations in the maternal and fetal compartments. Almost 7.3 kg (16 lb) of a typical (mean) weight gain come from the fetus, placenta, amniotic fluid and growth of the uterus and breasts; another 5 kg (11 lb) are from general growth of the mother's body and storage of nutrient reserves.[11] This is consistent with suggestions for healthy women by the Committee on Maternal Nutrition of the National Research Council for a 12.5-kg (27.5-lb) weight gain[11] and by the Committee on Nutrition of the American College of Obstetricians and Gynecologists for a 10- to 12.3-kg (22- to 27-lb) weight gain.[12] Generally, little weight gain occurs in the first trimester. The last two trimesters are usually accompanied by an average gain of 0.34 to 0.40 kg per week (0.75 to 0.88 lb per week).[13] One function of weight gain during pregnancy is to provide stores of energy (in the form of fat laid down under the influence of progesterone) that serve as a protective energy buffer for the fetus. Thus, emphasis need not be placed on a precise, absolute weight gain for each week of pregnancy. Instead, suggested weekly increments should be viewed as guidelines.[14]

Optimal weight gain during pregnancy is related to prepregnancy body build.[15] Consequently, the 10- to 12.3-kg recommendation is only applicable for women of average build. Optimal weight gain for overweight women is only about half of the optimal weight gain for very thin mothers (Figure 1). Regardless of body build, maternal weight gains of less than 6.8 kg (15 lb) are associated with increased perinatal mortality rates that result from a direct effect on the fetus and probably not from maternal acetonemia.[16] Pregnancy should never be a period of weight reduction, even in obese persons. Conversely, a weight gain of more than 14.6 kg (32 lb) is associated with an increase in perinatal mortality regardless of body build.[15] Within these wide weight guidelines, undue emphasis should not be directed to weight gain; instead, the long-standing recommendation, "eat to appetite,"[17] should be encouraged.

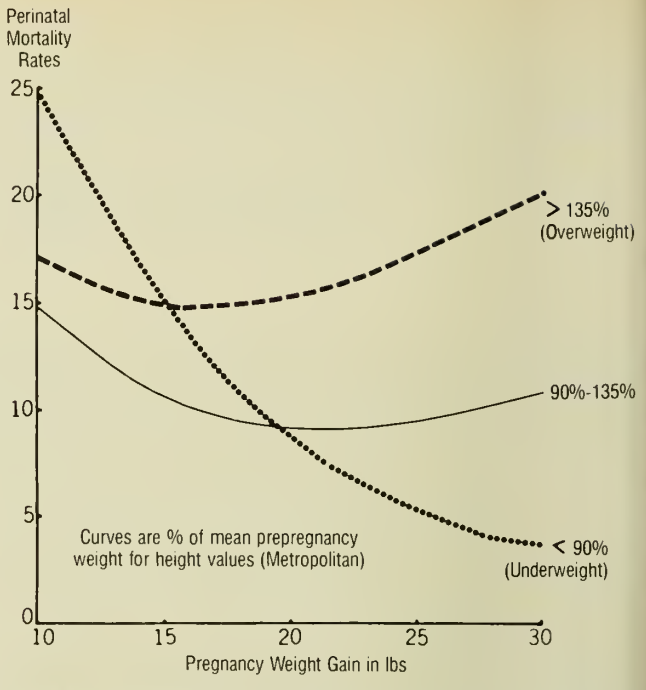

Figure 1.—Relationship of perinatal mortality rates to pregnancy weight gain according to maternal prepregnancy weight. (Perinatal mortality rates are expressed as infant deaths per 1,000 births.) (Modified from Naeye.[15])

Vitamins and Minerals

Opinion diverges regarding the value of vitamin and mineral supplementation during pregnancy. This results from different understandings of physiologic function during pregnancy. The physiologic changes of pregnancy are viewed either as adaptations to physiologic stress imposed by the fetus[18] *or* as adjustments to the process of fetal growth[11]—the differing views prompting different attitudes toward nutritional supplementation. "Adaptation to stress" implies the advisability of a nutritional response to an essentially undesirable situation. Alternatively, "adjustment to fetal growth" implies accommodation to an essentially normal process. The "stress" interpretation assumes obligate fetal requirements beyond those of a healthy nonpregnant woman. Yet it is clear that clinical standards held normal for nonpregnant women cannot be used as a standard for pregnant women. For example, plasma volume increases a maximum of 50% at the 34th week, the glomerular filtration rate increases about 60% and gastrointestinal motility generally decreases. These changes and the accompanying fall in serum vitamin and mineral concentrations may be viewed as a normal "adjustment" to pregnancy. This latter view is supported by the inability of experimental studies to detect a beneficial response of vitamin and mineral supplementation in pregnancy.[19]

Routinely supplementing iron to prevent anemia during pregnancy is widely advocated in the United States.[13,20] Reassessment of this policy has been advocated by the World Health Organization[21] and others[11,22]; new concerns have developed about high-dose iron supplementation and its potential association with intrauterine growth retardation.[23] During pregnancy, total erythrocytic volume rises an average of 250 ml over nonpregnant values. With supplemental iron throughout pregnancy, erythrocytic volume increases by 400

ml. Due to the more rapidly increasing plasma volume, mean hematocrits reach a nadir at 32 weeks' gestation. This fall is about 18% without iron supplements and is lessened to 13% with supplements.[13] To achieve maximum hemoglobin concentrations during pregnancy, total iron requirements are 600 to 800 mg of elemental iron.[13] This can be achieved by administering throughout pregnancy 30 to 60 mg a day of elemental iron.[3] Women who are known to have iron deficiency or who are at risk for anemia on the basis of poverty, adolescence or previous anemia should all receive iron supplementation.

Folate is required for not only the augmented maternal erythropoiesis of pregnancy, but also for DNA synthesis in the cells of all rapidly growing tissues such as the fetus and placenta. During normal pregnancy, serum folate levels decline progressively. This is partly due to increased urinary excretion. Although low serum folate levels (less than 3 ng per ml) occur in 20% to 25% of otherwise normal pregnancies, an associated megaloblastic anemia is uncommon in the United States.[24] Food sources encouraged during pregnancy should include those rich in folic acid, such as leafy vegetables, liver and, to some extent, nuts, cheese, eggs and milk. Because of folic acid's ready availability in the diet, many authorities stop short of recommending routine supplementation.[11-13, 22] Low-dose folic acid supplementation may reduce the incidence of neural tube defects in women who have had a prior child with a neural tube defect.[25,26] Before routine supplementation can be recommended, further confirmatory studies are necessary. When there is concern about a diet's adequacy for folic acid, a daily supplement of 800 μg is appropriate.[3,13]

Calcium metabolism adjusts during pregnancy to progressively promote maternal calcium retention. This begins during the first months of pregnancy, well before fetal skeletal mineralization, which begins in the third trimester. At term, a fetus stores about 27 grams of calcium, and maternal skeletal stores would be reduced by that amount if not replaced from dietary sources.[27] The recommended daily allowance of calcium during pregnancy is 1,200 mg, an increase of 400 mg over that for nonpregnant women.[3] Intake of calcium at this level should begin in the first trimester. Dairy products are the principal source of calcium in most diets. (One quart of milk contains exactly 1,200 mg of calcium.) Women who do not consume a similar amount of milk or dairy products will require supplementation. Vitamin D's importance in calcium metabolism is recognized, and one quart of vitamin D-fortified milk is sufficient to meet the recommended daily vitamin D requirements of pregnancy.[3]

The edema of pregnancy can be unpleasant but attempts to treat this condition with sodium restriction or diuretics are ill-advised, though common. Edema of pregnancy is physiologic, occurring in about 35% of normotensive women.[28] Salt restriction is not effective in managing preeclampsia, and diuretics have adverse effects.[29] Until the role of sodium in preeclampsia is clarified, pregnant women can use salt to taste.

Blood levels of most other vitamins and essential trace minerals are reduced during pregnancy, but whether this represents a deficiency or a physiologic change is speculative. Supplementation of these substances within the recommended dietary allowances[3] (for example, with the common prenatal multivitamin) probably is harmless and may be beneficial.[30]

Drug Exposure

Pregnant women want to know whether a drug will "hurt" their baby. Less concern relates to adverse maternal drug effects that have a specific relationship to pregnancy, such as tetracycline-induced acute fatty liver[31]; fortunately, such effects are rare. In spite of thousands of drugs available to physicians, relatively few have proven adverse fetal effects (Table 1).[32] Establishing the absolute safety of any drug during pregnancy is virtually an impossibility. Animal and in vitro study systems may yield results that are not applicable to humans. An uncommon occurrence with grave clinical results may not be detectable in human follow-up studies with fewer than many thousands of subjects. Studies such as these should be continued, but they are expensive and can be plagued with problems of bias. For these reasons, the standard for drug safety has become long-term observation of millions of women who have used the drug in question without ill-effects to their pregnancies. Decisions about other newer drugs often cannot be made with assurance because the data are insufficient. When in doubt, clinicians should consult existing drug catalogues.[33,34] Because of the difficulties in establishing safety, drug use during pregnancy should be limited whenever possible.

Interest should extend from prescription medications to social drugs such as alcohol, the most common proved human teratogen. Abstinence from social drugs offers pregnant women the greatest positive opportunity to modify their health and that of their fetus.

Alcohol

Maternal alcoholism has been clearly established as a severe risk for what is now known as the fetal alcohol syndrome.[35-37] It occurs in about half of the offspring of women with alcoholism, with an incidence in the United States of about 1 per 1,000 live births.[38,39] The principal anomalies include the following[40]:

- *Intrauterine growth retardation.* The pattern of growth retardation is generally symmetric, with proportional decreases in length, weight and head size that persist into infancy and probably into adult life with minimal potential for "catch-up growth."
- *Facial anomalies.* These are typically midfacial hypoplasia.
- *Mental retardation.* The IQs of children with the fetal alcohol syndrome have a broad range but seem to average about 70. In addition, minimal brain dysfunction with hyperactivity, decreased attention span and learning disabilities is common.[41]
- *Other.* Other associated anomalies have been reported, including cardiac septal defects and genitourinary anomalies.

While the severe risks of heavy alcohol consumption are definite, dangers from light drinking are less well established. The behavioral effects of moderate maternal alcohol consumption are difficult to measure in neonates and may only be apparent years later when schooling begins.[41]

Questions on drinking must be included in the routine evaluation. A physician's responsibility is to inform patients of the severe risks of heavy drinking and the potential danger of moderate drinking. Pregnant women with problems of heavy alcohol use should be encouraged to enter a treatment pro-

TABLE 1.—*Major Effects of Maternal Drug Use on Offspring* *

Drug	*Major Effects on Offspring*
Proved Human Teratogens†	
Thalidomide	Phocomelia
Phenytoin, trimethadione	Craniofacial and skeletal defects
Warfarinlike anticoagulants	Impaired nasal and optic development, epiphyseal stippling
Folic acid antagonists (aminopterin, methotrexate)	Cranial and skeletal defects
Androgens, some progestins	Masculinized genitalia (in female embryos)
Diethylstilbestrol	Genital tract abnormalities
Mercury	Central nervous system defects
Ethanol	Facial and central nervous system abnormalities
Suspected Human Teratogens‡	
Lithium carbonate	Cardiac defects (Ebstein's anomaly)
D-penicillamine	Connective tissue disorder (cutis laxa)
Benzodiazepines	Facial clefts
Oral contraceptive drugs	Limb and cardiac defects
Cancer chemotherapeutics	Varied effects
Nonteratogenic Adverse Drug Effects	
Aspirin	Premature closure of ductus arteriosus
Propranolol hydrochloride	Hypoglycemia, growth retardation
Thiazide diuretics	Thrombocytopenia, hypokalemia, hyponatremia, hyperbilirubinemia
Primidone, trimethadione	Depletion of vitamin K-dependent clotting factors
Chloramphenicol	Gray baby syndrome
Warfarin	Abnormal bleeding
Aminoglycosides	Auditory-vestibular nerve toxicity

*Modified from Scialli.[32]

†Unequivocal evidence links these drugs to human teratogenesis. While other drugs are probably teratogenic, supporting evidence is incomplete or lacking.

‡Data for the teratogenic effects of these drugs may be conflicting or incomplete. When more data are available, the teratogenic effects for these drugs may be proved.

gram to increase the likelihood that they will be able to abstain during pregnancy.[42]

Tobacco

The adverse effects of maternal smoking on human reproduction are extensive.[43,44] One of the most common neonatal findings in cases of maternal smoking is symmetric growth retardation.[45,46] These children remain smaller as adolescents and have significantly more behavioral problems, learning disabilities and poorer school performance.[47-49] Many other obstetrical complications are also increased in smokers. Included are selected congenital malformations,[50,51] abortion,[50,52] placental abruption and a substantial overall increase in perinatal mortality rates.[53] These untoward effects are produced, in part, by nicotine, which stimulates the sympathetic ganglia and releases catecholamines from peripheral nerve endings and the adrenal medulla. The increased maternal catecholamines reduce uterine blood flow that in conjunction with elevated levels of carboxyhemoglobin produces a fetal state of chronic oxygen deprivation and stress.[54,55] Indirect evidence suggests that the carcinogenic substances in tobacco smoke may act as transplacental carcinogens, increasing the liability of the offspring of smokers to tumors in adulthood.[56] Pregnant women should discontinue smoking at least for the duration of pregnancy.[57]

Caffeine

The Food and Drug Administration has recommended that pregnant women avoid or minimize intake of caffeine because animal studies indicate it causes birth defects in animals. This warning has been criticized because safe levels of caffeine were not defined,[58,59] and properly designed human studies have failed to show any adverse pregnancy effect associated with maternal coffee consumption.[60] In spite of the paucity of information on women showing adverse pregnancy effects of caffeine use, some pregnant women may wish to reduce their consumption. These women should be made aware of the significant amount of caffeine found in tea, cocoa and other foods and beverages.

Marijuana

Data regarding the impact of smoking marijuana during pregnancy are difficult to interpret due to the small size of the reported series. However, there are no findings to suggest that marijuana is teratogenic in animals or humans.[33(p269),61] Several studies have suggested that marijuana consumption during pregnancy leads to intrauterine growth retardation, premature labor, meconium staining, dysfunctional labor and features suggestive of the fetal alcohol syndrome.[62-64] However, lack of satisfactory control for potentially confounding factors (multiple drug use, socioeconomic status and the like) makes interpretation of these results difficult.[65] In mice, prenatal exposure to cannabinoids results in alterations of endocrine function and brain amine levels in adulthood. These effects, which are not evident at birth, become apparent only when the offspring themselves begin reproducing.[66,67] Unless substantial long-term studies exonerate maternal marijuana consumption from untoward effects on fetal growth and development, patients should be strongly advised against consumption during pregnancy.

Perinatal Infection

Concerns about the risks of infection are heightened for women during pregnancy. Although serum immunoglobulin

levels are decreased[68] and cell-mediated immune responses are suppressed in pregnancy,[69,70] the clinical significance of these findings remains conjectural, and pregnancy data do not support a substantially increased incidence of viral infection.[71] Nonetheless, the proportion of women with an infection that may have direct adverse consequences on a fetus is impressive, about 14% for the TORCH complex alone.[72] (TORCH is an acronym for *t*oxoplasmosis, *o*ther [syphilis, chickenpox, hepatitis B and the like], *r*ubella, *c*ytomegalovirus and *h*erpes simplex virus.) Further, approximately 15% of women are colonized with group B *Streptococcus*[73] and as many as 5% to 10% harbor *Chlamydia trachomatis* in the cervix.[74]

For members of the TORCH complex, the general measures for diagnosis and for maternal therapy are similar. The major health risk is confined to the fetus and infant. Maternal signs and symptoms that suggest infection should be immediately reported to a physician; symptoms alone are not reliable for diagnosis, however. Instead, maternal infection must be documented by serology or by viral isolation of the herpes simplex virus. Generally, accurate serologic diagnosis of current infection requires the finding of a significant rise in antibody titer. Serum should be obtained immediately when there is a suggestion of infection. A rise in antibody titer is usually found in a second sample obtained two to three weeks after onset of infection. Except for cases of syphilis and toxoplasmosis, maternal therapy is supportive with no special therapy available. If maternal infection is documented, at present, techniques are not available to diagnose the presence or absence of corresponding fetal infection. Amniocentesis for viral recovery is not predictive of an affected fetus. At birth, infant serology and culture will verify a microorganism, if present. Except for neonatal herpes simplex infections that produce high mortality and morbidity, infection with other TORCH agents does not generally result in apparent neonatal disease. However, late sequelae to these infections can result in damage to the perceptual organs and the brain, which would not be recognized until later in life.[72] Infectious control should be directed at prevention by immunization and minimizing exposure, if possible.

Maternal cytomegaloviruses, the most common cause of intrauterine infection, occur in about 13% of pregnancies[75] and 0.5% to 2.5% of live births.[76] Less than 5% of infected infants have classic cytomegalic inclusion disease (hepatosplenomegaly, microcephaly, chorioretinitis and so forth); however, subtle learning disorders and auditory deficits may be more common.[77] Much remains to be known about the means of transmitting cytomegalovirus between adults. The occupational contact of pediatric health-care workers does not appear to confer greater risks for infection.[78] At this time, screening for cytomegalovirus at the initial prenatal visit appears to be of negligible value.[79] The eventual development of an effective vaccine is the most promising avenue for reducing risk.

Toxoplasmosis, an infection caused by the protozoan parasite *Toxoplasma gondii*, is rare but potentially preventable during pregnancy. Congenital toxoplasmosis is associated with chorioretinitis, hydrocephalus and intracranial calcification plus a wide range of less severe manifestations.[72,80] Exposure to the parasite is by ingesting uncooked meat containing tissue cysts, or from oocysts in cat feces. Proper food handling and treatment of cat feces will avoid infection in susceptible women (Table 2). Routine serologic screening may prove to be efficacious in the future, but, at this time, quality control is apt to be haphazard and screening is not recommended.[80] For women known to have a primary infection during pregnancy, antimicrobial treatment appears to be effective in reducing fetal susceptibility.[81]

TABLE 2.—*Methods for Preventing Maternal Toxoplasmosis* *

Cook meat to ≥66°C (150°F), smoke it or cure it in brine
Avoid touching mucous membranes of the mouth and eye while handling raw meat
Wash hands thoroughly after handling raw meat
Wash kitchen surfaces that come into contact with raw meat
Wash fruits and vegetables before consumption
Prevent access of flies, cockroaches and so forth to fruits and vegetables
Avoid contact with or wear gloves when handling materials that are potentially contaminated with cat feces, such as cat-litter boxes, or when gardening
Disinfect cat-litter box for 5 minutes with nearly boiling water

*Modified from Wilson and Remington.[80]

Herpes simplex virus acquisition by a fetus is rare (less than 0.05% of live births), occurring predominantly during birth through the vagina.[72] Disseminated and localized central nervous system disease affects most cases and severe central nervous system damage is common among survivors.

Pregnant women with a history of genital herpes or those with an undiagnosed genital lesion should notify their physicians. Whenever possible, in women without a history of genital herpes, viral cultures should be taken from all genital lesions. During pregnancy, suppression of recurring genital herpes with oral acyclovir is not indicated.[82] Women with recurrent genital herpes can expect the recurrences to increase as pregnancy progresses.[83] Asymptomatic viral shedding can occur from the cervix and vulva without a visible lesion.[84] This has prompted recommendations for viral screening cultures during the last month of pregnancy.[85] However, this is controversial because the cost is great and estimates are that with current techniques a maximum of only a fourth of infant infections could be averted.[86] At the onset of labor, all patients should have a careful inspection for herpetic lesions of the vulva, vagina and cervix. Because of the risk of asymptomatic viral shedding and ascending herpetic infection, vaginal examinations and instrumentation should be kept to a minimum in women with a history of genital herpes. Patients in labor who have a definite herpetic lesion (or an undiagnosed lesion suggestive of genital herpes simplex virus) should have a cesarean delivery, even in the absence of a positive viral culture, regardless of the duration since the rupture of membranes.

Cases of maternal and fetal rubella are rare, occurring annually in fewer than 50 infants in the United States. More than 30% of infants from pregnancies infected during the first trimester are seriously affected with a wide range of defects, including congenital deafness, cataracts and blindness and severe heart defects.[72] From 10% to 20% of reproductive-age women are seronegative for rubella antibodies. Seronegative, nonpregnant women of childbearing ages should be immunized and warned to avoid pregnancy for three months following vaccination.[87] Opportune settings include routine gynecologic and family planning facilities and during hospital stay after childbirth or abortion.

At present the recommendation is not to screen routinely for prenatal group B *Streptococcus* or *C trachomatis*. This relates to uncertainty regarding the proper timing for screening due to high maternal recolonization rates and the potential adverse effects from treatment of many pregnant women or infants who were colonized, but in whom disease would not have developed.

Exercise

Estimates are that 25 million Americans, or 10% of the population, jog regularly.[88] Pregnant women who jog or engage in other regular strenuous exercise are justifiably interested in its effects on their health and that of their fetus. Further, some competitors who become pregnant plan to continue strenuous sports and are interested in the effects that should be anticipated in their performance. Little is known about the effects of exercise on any of the specific pregnancy outcomes. However, insight into the potential consequences of exercise can be gained by considering its effects on maternal physiology. This subject has been recently reviewed by Lotgering and co-workers.[89]

Maternal oxygen consumption by organs other than the uterus is not increased substantially during pregnancy. Although maternal oxygen consumption near term increases by 16% to 32%,[90,91] most of the increase is related to uterine mass. Thus, exercise in the sitting position does not increase oxygen consumption more than with similar exercise in the nonpregnant state.[89] Because of the increased oxygen requirements of weight-bearing (the pregnant uterus) for treadmill exercise, however, increases in oxygen consumption are greater during pregnancy.[92] These data suggest that exercise efficiency is not altered substantially by pregnancy.

Blood flow to a pregnant uterus decreases immediately after the onset of exercise.[93,94] Decreases as great as 36% have been reported.[95] However, the implications of reduced oxygen availability to the fetus may not be valid. The hematocrit increases during exercise in association with a fall in plasma volume and increased glomerular filtration.[96] Further, in sheep, blood flow under the influence of catecholamines is redistributed from the myometrium to the placental site,[97] and a reduction in oxygen availability has not been noted.[95] Some studies of pregnant ewes[95,96] have indicated a significant fall in fetal oxygenation during maternal exercise. However, in these studies blood gas values were not corrected for the raised temperature that accompanies exercise.[89] In other studies in which a raised temperature was corrected for, only a small reduction in fetal oxygenation was found.[99]

Fetal heart rate studies have provided no consistent evidence of fetal distress during or after jogging or other exercise. Whereas some investigators noted modest fetal heart rate increases with maternal exercise,[100,101] others found fetal bradycardia with exercise.[102] Although exercise can induce fetal heart rate patterns that are consistent with fetal distress, the abnormal fetal heart rate patterns are not directly caused by the exercise. Instead, the exercise "unmasks" another condition such as nuchal cord,[103] placental insufficiency[103,104] and the like that has compromised the fetus. This has prompted some clinicians to suggest that the response of a fetal heart rate to maternal exercise could be used as a test of fetal well-being.[103,104] Hauth and associates detected no difference in the incidence of fetal heart rate abnormalities in seven pregnant women after jogging on a total of 30 separate occasions.[105] At this time, limited studies do not support any adverse effect of maternal exercise on a fetus.[106]

Maternal exercise and physical fitness may be associated with a reduced duration of labor. Pomerance and colleagues found shorter labors for physically fit multigravid women, but not for fit nulliparous women.[107]Erkkola noted shorter spontaneous labors among women with above-average work capacity.[108] Collings and co-workers[101] detected no differences in the duration of labor of 12 women who engaged in a regular aerobic exercise program compared with 8 other women who did not exercise. The positive association between maternal exercise and shortened labor must be interpreted cautiously. Studies have not detected a reduction in the length of the second stage, that part of labor dominated by voluntary muscular activity which would appear most responsive to physical conditioning. Further, these studies did not control for analgesic use, which may be different in women who exercise.

Exercise conditioning can advance with training during pregnancy; postpartum, athletes should not expect a reduction in their athletic abilities. During pregnancy, exercise elicits the same metabolic and cardiovascular responses as it does in the nonpregnant state.[109] Erkkola noted a significant increase in the physical work capacity of randomly selected pregnant women who engaged in regular strenuous activity compared with nonexercising controls.[110] Olympic athletes who had had children judged their physical and functional condition to be better after childbirth than before pregnancy.[111]

Work

Newly pregnant women who are employed outside the home are confronted with a decision: Should I stop working before the end of the pregnancy and, if so, when? Considering that nonsalaried housekeeping and child rearing can be just as strenuous as other salaried employment, rational solutions are difficult. Available data and advice from physicians have been conflicting. Federal disability legislation has added new financial considerations that temper medical advice. This confusion is superimposed on prevalent societal expectations that have held sway for previous generations and vary widely across cultures.[112]

Available information is difficult to interpret for three reasons. First, there are considerable differences in the kinds of work women do. Second, studies carried out in different countries at different times would be expected to have different results. Third, employed women vary from nonemployed women in several aspects such as education, parity and the use of health services.[113]

More recent studies[114-116] have not supported an association between employment during pregnancy and adverse pregnancy outcomes that was found with earlier data.[117,118] Stewart noted more prematurity, low-birth-weight infants and perinatal deaths among the pregnancies of British women who were employed in Northamptonshire during their pregnancy.[117] If work ceased before 28 weeks' gestation, adverse outcomes were less frequent among the women who were employed. Naeye and Peters presented compelling data from the Collaborative Perinatal Project of the National Institute of Communicative Disorders and Stroke that suggested a significant progressive effect on birth weight by duration of employ-

ment when it continued past the 28th week of gestation.[118] The pattern of low birth weight suggested reduced uteroplacental blood flow. Murphy and associates had opposite results and different conclusions[115] using British data from the Cardiff Births Survey. Adverse pregnancy effects were all more common for nonemployed mothers, and the increase in premature births for prepregnancies of nonemployed mothers was statistically significant. Among employed mothers, the nature of the work (sedentary, nonsedentary) and time of stopping work did not significantly affect the results. A recent French national birth survey[113] had findings similar to the British study. Two hypotheses have been advanced to explain the superior pregnancy performance of the employed mothers in these two studies. First, by virtue of their ability to be employed, working mothers generally should be expected to be healthier and have less adverse pregnancy outcomes. Second, social contacts are enhanced for working women and their access to medical care is greater.

These relatively sparse and conflicting findings make it difficult to arrive at specific recommendations for the continuance of work during pregnancy. In addition to the medical consequences of work during pregnancy, the greater participation of women in the work force and passage of the Pregnancy Discrimination Act (PL 95-555) magnify the economic impact of physicians' recommendations about whether or not to continue employment during pregnancy.

The basic principle of the Pregnancy Discrimination Act is that pregnancy and related conditions must be treated in the same nondiscriminatory fashion as any other disability or medical condition. Basically, the law prohibits employers from illegally eliminating pregnant women from certain jobs and protects pregnant women's disability insurance benefits if the company has a disability plan and the pregnant worker is medically disabled. Because the law does not define disability or place time limits on the benefits, physicians will be asked to certify the extent and duration of the pregnancy-related disability.

As part of a physician's (and employer's) responsibility to minimize the effects of a pregnancy-related disability, every effort should be made to ensure that the specific job is safe and its environment is nontoxic to a mother and her fetus. When in doubt, regional consultants are available at the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA).[119]

The American College of Obstetricians and Gynecologists (ACOG) has drafted a principle applicable to most women during their pregnancies: "The normal woman with an uncomplicated pregnancy and a normal fetus in a job that presents no greater potential hazards than those encountered in normal daily life in the community may continue to work without interruption until the onset of labor and may resume working several weeks after an uncomplicated delivery."[119] The principle is consistent with the traditional six- to eight-week window of per se disability (beginning two weeks before delivery and continuing until six weeks' postpartum) that surrounds the time of delivery for most normal pregnancies.

Each situation should be interpreted individually. Guidelines for continuing various levels of work during pregnancy have been established by NIOSH and ACOG (Table 3).[120,121] For most employment, these guidelines support the concept of continued employment until delivery. Although this concept has been acknowledged by most large firms, this may not be the case in small companies and a physician may be thrust into a new role as patient advocate.[122]

TABLE 3.—*Guidelines for Continuing Various Levels of Work During Pregnancy**

Job Function	*Week of Gestation*
Secretarial and light clerical	40
Professional and managerial	40
Sitting with light tasks	
Prolonged (>4 h)	40
Intermittent	40
Standing	
Prolonged (>4 h)	24
Intermittent	
(>30 min/h)	32
(<30 min/h)	40
Stooping and bending below knee level	
Repetitive	
(>10 times/h)	20
Intermittent	
(<10 >2 times/h)	28
(<2 times/h)	40
Climbing	
Vertical ladders and poles	
Repetitive	
(≥4 times/8-h shift)	20
Intermittent	
(<4 times/8-h shift)	28
Stairs	
Repetitive	
(≥4 times/8-h shift)	28
Intermittent	
(<4 times/8-h shift)	40
Lifting	
Repetitive	
>23 kg (50 lb)	20
<23 >11 kg (25 lb)	24
<11 kg	40
Intermittent	
>23 kg	30
<23 >11 kg	40
<11 kg	40

*Modified from *The Journal of the American Medical Association* (1984:251:1995-1997). Copyright 1984, American Medical Association.

Comment

Health maintenance in pregnancy extends beyond the highlights discussed in this article. Personal health maintenance, broadly interpreted, begins with preconceptual contraceptive planning and continues through to the choice of a site for delivery. The fundamental aspects of personal health maintenance are generally simple, but the effects of disease prevention and peace of mind may be substantial. Obstetricians should embrace these concepts to achieve optimal outcomes for their patients.

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Personal Health Maintenance for Children

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The foundations for lifelong responsibility for personal health maintenance are laid down in childhood. Personal health maintenance for children is important for a healthy childhood, for a healthy adulthood and for the development of positive values about health, personal health responsibility and the use of health services. Present knowledge in this area is weak but growing. Five areas of development are highlighted: (1) the cognitive understanding of health and disease, (2) a psychological sense of control over health, (3) parental and media influences on health behaviors, (4) school health education and (5) training by health professionals about self-management of childhood illness and health services usage patterns. Implications for current practice are developed.

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The health of children in the United States has undergone dramatic improvement since the turn of the century. Because of the applications of our rapidly increasing knowledge through personal and public health practices, sharp reductions have occurred in infant mortality, morbidity and mortality from the infectious diseases, malnutrition, diarrheal diseases and the complications of many metabolic disorders.[1] The revolution in biology has resulted in a revolution in child health.[2]

These advances present new challenges. The dramatic reductions in morbidity and mortality of the recent past contrast with further improvements that will come more slowly; additional new approaches to fostering child health will be necessary. Personal health maintenance—the theme of this special issue—now becomes a major objective for children, as well as for adults. The pursuit of this goal offers the possibility of further improvement in the quality of life and longevity.

As we turn our attention to health promotion and disease prevention for children, four issues merit consideration:

1. Personal health maintenance is important for a healthy childhood. Children's own health promotion activities, or those provided for them by their parents or other caretakers, can have an impact on fostering improved health during childhood. For example, some major health threats to childhood health are amenable to preventive approaches:
   - fluoridation and oral hygiene to reduce dental caries,
   - safety belt use and alcohol abstention to reduce automobile injuries,
   - immunizations to retain the gains and to reduce further the major childhood infectious diseases.
2. Personal health maintenance for children is important for healthy adulthood. Although information is quite limited, there is a consensus that the origins of many of the illnesses of adulthood have their roots in the health behaviors of childhood and adolescence. Dietary habits, physical fitness levels, smoking and substance abuse all have their roots primarily in childhood.
3. Personal health maintenance for children is important for the development of positive values about health and personal health responsibility. Although education does not stop in childhood, childhood is the developmental period in which society sanctions the formal education of its members about health and sickness. Through families, schools and communications media, society shapes a child's view of what to expect about health, what are solutions for health problems and what are consequences of behaviors. Attitudes about health issues—such as fluoridation, health insurance, pollution control—are heavily shaped in childhood.
4. Personal health maintenance for children is important for the development of responsible health service usage behaviors. The origins of many adult patterns of health services use appear to develop in childhood.[3] For example, adult asymptomatic (preventive) dental care is most strongly associated with regular family dental visits as a child.[4] The well-known pattern of overusage of primary care resources by a small percentage of adult clients already has its parallel in the overusage of school nurses by some elementary and high school students.[3,5] Adult usage behavior is at least partially shaped during childhood.

Despite the seemingly obvious importance of this topic to

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society, there have been relatively limited research and demonstration programs. Several factors have contributed:

- The limited research base of adult health promotion and preventive medicine has yet to be extended into the childhood years. A developmental framework for health promotion and disease prevention is still lacking.
- The developmental changes in a child's first 20 years prevent a singular approach. Personal health responsibility for infants and preschoolers differs from that of school age children, which differs yet again from that of adolescents. These rapid changes in children's capacities hinder systematic formulations.
- There is ambiguity concerning who has the responsibility for "personal health maintenance for children." Certainly children should be encouraged to assume responsibility appropriate for their developmental levels, but, to a large extent, parents and society are responsible for the personal health maintenance of children. Much of children's health promotion material is directed at parents. One may ask whether personal health maintenance is *for, with* or *by* children.
- Child health professionals have relatively little training in fostering personal health maintenance and most devote little time to it in their practices. For example, Reisinger and Bires[6] show that only 8.4% of the average 10.3-minute primary care visit is for "anticipatory guidance." Moreover, present reimbursement systems provide few incentives for pediatric health promotion and disease prevention efforts.

The title of this article captures the duality of the medical profession's responsibility to reinforce children's personal health maintenance behavior and to assist them in its development. The medical profession must address the issues of setting early patterns of personal health maintenance during childhood. What are the antecedents of good and poor adult health habits, and how can we foster positive personal health responsibility in children, for their present and future health?

For children to develop sound health behaviors, they must have a realistic understanding of their role in preventing disease and learn to be active participants in maintaining their health. How to foster these objectives is not clear. Rather than attempting to provide only practical considerations, the bulk of this essay will examine what is known about children's understanding of health and illness and how their health behaviors are developed passively or actively. Unfortunately we must state at the beginning that the research literature on children's acquisition of health-related concepts, beliefs, attitudes and behavior is relatively undeveloped, but a knowledge base is growing.[7] In this essay we will examine five factors that appear to play a positive role in a child's development of personal health maintenance:

- The development of a child's cognitive understanding of health and illness;
- The origins of the psychological sense of control over health;
- The influence of parents and media on health behaviors;
- The role of formal school health education;
- The training by health professionals about specific childhood illness self-management and health services usage.

We hope that the understanding of these topics will lead practitioners to apply their knowledge in increasingly effective ways.

Children's Understanding of Health and Illness

Personal health maintenance implies a cognitive awareness that behavior is linked to health. While this is taken for granted in adults, in children this association must be learned.

Several investigators have interviewed a wide age range of children about their knowledge of health and illness. The results seem to give consistent findings. Perrin and Gerrity,[8] for example, showed that kindergarten children attribute the cause of illness to magic or to a consequence of their own transgressions (egocentric causation); fourth graders believe that germs cause illness (concrete causation), and only by the eighth grade do children begin to understand the multiple factors and complexity of host-agent interactions in causing illness (formal causation). Weithorn and Campbell[9] studied the competence of children to make appropriate and informed decisions about health care treatment. They found that 14-year-olds performed as well as older subjects (18- and 21-year-olds), but 9-year-olds were less competent in their abilities. These age trends are consistent with a Piagetian framework of cognitive development. Nagy,[10] Goochman[11] and others with different developmental orientations also report that at ages 12 to 13 there is maturation of adult conceptualizations of illness.

Three important factors can be derived from understanding children's developmental reasoning about health and illness. First, young children (younger than 7 years) have a strong but unrealistic egocentric belief in the causation of illness. This coincides with the many clinical reports of young children blaming themselves for their illnesses, attributing sickness to disobedience of parental instructions and an admission to hospital to rejection or punishment.[12] These and similar observations suggest the importance of the following: clearly explaining illness to young children, emphasizing their nonresponsibility; not being too theoretic in explaining illnesses; reassuring them of support to prevent loss of self-esteem, and limiting expectations that young children will initiate health-promoting behavior or understand the consequences of their actions. Physicians tend to overestimate the sophistication of young children.[13] The absence of a child's verbalization about the cause of illness, or an adult's desire not to directly address a child about his or her illness does not mean the child has not interpreted the experience. An adult's views on self-responsibility for health promotion can be easily misinterpreted by a very young child's egocentric view to be blaming rather than empowering.

Second, the data consistently show that children older than 12 years are able to reason intellectually about illness in a manner similar to adults. (This is not to say all children are able to reason the same as adults, or that all adults use sophisticated formal logic when confronted with illness.) Yet, professionals often approach older children as if they cannot fully grasp the concepts of illness and health or assume major personal responsibility for their own health. Perrin and Perrin's[13] data suggest that physicians tend to underestimate the sophistication of older children. The relatively young age of cognitive maturing stands in contrast to the prolonging of adolescence and parental dependency seen in our society.

Third, a possible implication of these developmental findings is that children before they are 12 are believed to be limited in their ability to take personal responsibility for their

health because they cannot fully understand illness. This belief is in error. It flows from a simplistic interpretation that cognition alone determines behavior. Children in the 7- to 12-year age range can learn specific health-promoting behaviors, even if they do not fully understand the connections between illness and behavior. This age period corresponds to the age of learning rules—rules of games, rules of behavior, rote learning—without always having a full understanding of the reasons why. Health habits can be developed in this period. Brushing teeth, eating good foods, personal hygiene and physical activity can all be taught during this period. Children's reasoning may be somewhat concrete: "Brush away germs," "good foods prevent illnesses," "sugar causes tooth decay." Nonetheless, they have begun the process of assuming responsibility for their personal health.

The association of health cognition and health behavior is not synonymous. Many researchers have shown that child health knowledge and health behaviors are not strongly correlated.[11,14,15] Weisenberg and co-workers[15] conclude that health beliefs are unrelated to behavior and may represent parallel but not causally related developments in a person.

While a cognitive developmental framework provides useful age markers about a child's understanding of personal health responsibility, it is clearly limited. The association of cognition and behavior is not clear. Indeed, many adults operate in a manner similar to 7- to 12-years-olds: concrete rules for concrete health decisions. This framework does not help us understand the basis for variations in health behaviors. Why do some children respond one way to cigarette smoking and others another way, when both have the capacity to reason through the health implications similarly?

Children's Sense of Control Over Health and Illness During Childhood

Locus of control describes a psychological trait concerned with a sense of mastery over one's interaction with the physical and social world. In traditional locus of control models, persons are divided into those with an internal sense of control over events in their world (belief in personal responsibility), who will act on the world—that is, take a preventive health action—and those persons with an external (chance) sense of control over events, who will less likely act to influence their world. For adults, high internal locus of control has repeatedly been shown to be associated with more health-promoting behavior—smoking cessation,[16-18] losing weight[19] and wearing seat belts.[20]

Traditional bipolar (internal versus external) locus of control models have seemed inadequate to describe fully most persons' health motivations. Interest in the health locus of control construct has recently increased with the development of a *multidimensional health locus of control scale.*[21] This scale divides the locus of control construct into one internal and two external dimensions. The two external concepts, *powerful others* and *chance health locus of control,* differ in that the former measures the extent to which people believe that others such as doctors and parents can control their health, whereas the latter measures the degree to which persons believe that no one can control their health. This new set of psychological constructs captures the belief of many persons that illness and health are neither chance events nor in their control, but rest in the hands of powerful experts. For the first time, the locus of control literature suggests a direct motivational linkage to trust in health care providers. According to Wallston and Wallston,[22] persons who have strong beliefs in internal control and in the control of powerful others and weak beliefs in chance control are likely to develop advantageous health behavior.

In an attempt to determine the origins of health locus of control, Lau[23] conducted a retrospective study among 270 college students correlating adult health locus of control beliefs with childhood health habits and illness experiences. He found that adults who perceive themselves as having more personal internal control over their health went for regular medical checkups and participated in self-care health habits as children and had fewer childhood experiences with sick family members. Adults who had stronger beliefs in the efficacy of doctors had early and regular contact with medical professionals and fewer childhood experiences with sick family members. Adults who had strong beliefs in the role of chance in health outcomes were likely to have had many childhood illness experiences.

The results of this study suggest two important conclusions. First, positive childhood health behaviors (regular checkups and self-care habits) are predictive of a positive sense of control over one's health in adulthood. Thus, the encouragement of childhood health behaviors can lead to a positive sense of personal health responsibility in adulthood. Second, and more troubling, frequent childhood illnesses may lead to an inappropriate belief in the role of chance in health outcomes. This seemingly unusual finding appears to be consistent with the previously discussed cognitive developmental model. Young children with frequent illnesses, who may be given inadequate explanations, are likely to inappropriately fault themselves or magically credit others for their illnesses. Illness experiences do not necessarily lead to self-control over health and belief in powerful others, as a social learning model might predict. This phenomenon can be seen in an exchange with the 10-year-old son of one of the authors, who has asthma: When asked what he thinks of his pediatrician, he stated, "I don't want to see him again, because he never can cure me when I'm sick!" Interpreting childhood illnesses to children seems to merit more attention than many of us give, both as parents and as health care professionals.

Lau's work[23] must still be seen as somewhat preliminary; it is a retrospective analysis based on a limited college age sample. It does, however, begin to point out the importance of examining real life correlates of positive health locus of control concepts to understand the variability in children's assumption of positive health responsibility. Unfortunately, efforts to examine directly the origin of positive health locus of control beliefs in children have been limited by the relative unavailability of children's health locus of control scales.[24]

Our own pilot study[25] suggests that for 9- and 13-year-olds positive health behaviors—better nutrition, physical exercise, sleep, dental hygiene, refraining from smoking or alcohol use and injury prevention—were associated with strong belief in internal control and powerful others (doctors, parents) and weak belief in chance control of health. Developmental changes could be seen across the two groups. Nine-year-olds had greater belief that others controlled their health (either chance or doctor control), whereas the 13-year-olds' patterns begin to fit the expected adult model of a strong belief

in powerful others and a weak belief in chance. While only a pilot study, it does suggest that cognitive motivational patterns, even in children, may play a role in fostering personal health care behavior.

In a very practical area, that of injury prevention for children, one can see the importance of health locus of control beliefs. Although the literature on injury prevention programs for children is weak,[26] many injury prevention programs are directed at training children about the dangers they face. Fire drills, auto safety, pedestrian safety and swimming safety are all directed at enhancing children's personal sense of responsibility over their environment. The prevention of injury is one area in which children are taught (and in part learn through trial and error) to be responsible for their own actions. Indeed, one can note with irony that although most people refer to these injuries as "accidents," this is one of the areas in which parents most explicitly train their children. Physicians could play a larger role in this area than most do at present.[6] Safety is a major area of early health learning. Injury prevention is based heavily, though by no means exclusively, on a child's own internal sense of personal health responsibility.

Parental and Media Influences on Children's Personal Health Maintenance Behaviors

A third factor contributing to early patterns of personal health maintenance is the development of specific health-promoting behaviors during childhood. When the adoption of specific behaviors is influenced by external factors, social scientists refer to this as the socialization of behavior. While there are many sources for socialization of health behaviors as a child develops, we will focus on only two—parental and media influences.

There are numerous studies examining the congruence or incongruence between parents and children in health-related attitudes, behaviors and the use of services. Studies that look only at health beliefs or attitudes generally find weak or no relationships between children and adults. For example, Robertson and colleagues[27] found that elementary school children manifest more anxiety about illness, worry more about getting sick and believe more in medicine than do their parents. Campbell[28] who interviewed 264 children (ages 6 through 12) and their mothers found little congruence between mother-child pairs in their description of "illness." Mechanic[29,30] failed to show a strong relationship between the health beliefs of parents and the subsequent beliefs of their children when grown. Perhaps the developmental disparities of children and adults inherently limit the possible congruence of their health beliefs.

By contrast, some specific parental behaviors do show strong congruity. Parental smoking predicted high school and junior high school smoking in their children.[31,32] Competitiveness and aggressivity,[33] drinking,[34] obesity[35] and dental hygiene[36] all show significant positive associations between children and adults. Tyroler and associates[37] showed a high correspondence between mothers and children obtaining polio shots. Actual parental behavior would appear to be a relatively strong determinant of specific childhood health habits.

The mechanisms by which parents influence a child's behavior have not been established. Parents provide both a role model for their children and directly reinforce early health behaviors. However, the extant studies confirm what is found elsewhere in research on child-rearing and socialization, that parents are only one among many diverse influences on a child and that parental influence tends to diminish as children grow older.[7] Nonetheless, because many health-promoting behaviors appear to be established early, parental influence is quite important.

More attention should be paid by health professionals toward emphasizing the importance of greater parental supervision over early health behavior patterns. At present, most of our health-promoting messages only imply parental supervision, but do not directly emphasize it, nor do they offer specific help to parents in gaining compliance from their children. In their capacity as role models, it is fortuitous that behaviors that parents should be modeling will enhance their health as well as their child's. Parents have a positive role to play in a child's development of personal health maintenance.

The media, especially television, is also playing an increasing role in the development of children's personal health habits and knowledge about health. Smoking, drinking, drug use and abuse, nutrition, dental health, sexuality and violence are some of the key health behaviors directly influenced by television. The power of television as a possible educational force is enormous. Starting at 3 years of age the average American child watches 30 hours per week, or a total of 6,000 hours before beginning school; by high school the average child has watched a total of 15,000 hours of television (versus 11,000 hours for all formal education.)[38] Furthermore, the amount of TV watching is increasing. In a single year, a child might see 20,000 commercials![38]

Two Surgeon General reports have focused on television's impact on children.[39,40] Although television has great potential, both positive and negative, several issues should be of concern for fostering personal health habits for children. First, there is insufficient educational programming for children. Most television is not directed at children. The Federal Communications Commission (FCC) reported that in 1977-1978 only 2.6 hours per week of programming was devoted to children.[41] Second, despite the difficulties in researching the effectiveness of the media, both Surgeon General reports[39,40] emphasize the growing evidence that television does influence behavior. Children tend to imitate patterns seen on TV.[42] Aggressive behavior has been linked to television.[43] The media influences are of particular concern on issues such as violence,[44] auto safety[40] and alcohol and drug usage[45]—matters of great importance for a child's own sense of personal health. Third, younger children are developmentally unable to distinguish whether what they see on television is real or not. While older children are more resistant to TV programming and advertising, children younger than ages 8 or 9 do not have the full intellectual capacity to distinguish fantasy from reality; they are readily beguiled.[46] Fourth, advertising that is directed at children mostly concerns toys and food products.[40] Many of the toys are implicated in sex-role stereotyping and rewarding aggressive behaviors. Even more worrisome is the advertising for nutritionally inappropriate foods.[47] Television advertising heavily emphasizes snacks and processed foods that are often laden with sugars and salt. (Action for Children's Television, a child advocacy group, has recently filed a suit to label most advertised children's cereals as candies

because many contain 50% or more sugar.) Young children's vulnerability to advertising may inhibit the development of subsequent sound nutritional patterns. And, finally, watching television limits the time available for physical and other activities of children; it induces a physical passivity and often precludes other healthy outlets for social and intellectual development.

Television and other media appear to play a major role in the growth and development of children. The federal government through the Federal Trade Commission and the FCC must assume more responsibility for the media messages sent to children. For children relatively little progress has been made in the two decades since a former FCC commissioner referred to television programming as a "vast wasteland."

The development of children's health behaviors is constantly taking place as a result of various socializing pressures during childhood. Given the early onset of many "adult" behaviors, early influences are critical factors. The paucity and limited correlational nature of much of this research is noteworthy. We know that influence of parents and television increases the likelihood of the adoption of certain behaviors, but the relative contribution of the different socializing agents to specific behaviors seems elusive. It is not clear why some children adopt certain patterns of behavior, in contrast to others, when exposed to the same external messages. The socialization processes, possible sensitive periods, possible critical events and ties to cognitive understanding all remain relatively unexplored.

Influence of School Health Education on Early Patterns of Personal Health Maintenance

Because more than 95% of children and youths from 6 to 18 years can be reached via the schools, there has always been a strong rationale for using the schools as sites for formal instruction in health and hygiene. Health education has been a regular part of school life for decades, and earlier in the history of public education in this country it was considered one of the basic subjects.[48]

School health education programs vary greatly in quality and curriculum time. Health education textbooks constitute the main resources for such teaching and a review of these texts over recent years indicates a considerable improvement in their quality. Currently 17 states have a statewide textbook adoption law. Unfortunately, no systematic assessment has been made of their impact on improving behavior related to personal health maintenance.

Too often health education is fragmented. The Select Panel for the Promotion of Child Health[48] noted that whereas many voluntary groups and health agencies have developed teaching materials on specific topics especially for school use, the number of health problems deserving special consideration in the curriculum has become so great that many of these teaching aids can only be useful if they are part of a comprehensive and sequential health education program, which well-written textbooks attempt to provide. In the absence of a comprehensive program, school administrators under community pressure to "do something" about drugs, sex, smoking, alcohol or other problems too often respond with a hastily scheduled unit or a lecture to cover a specific problem. Fragmented education efforts of this kind are hardly an adequate response to the need for better health education. A systematic approach to teaching health, organized so as to encourage coordination with other subject matter and evolving sequentially through the school years in developmentally appropriate steps, is needed.

In many school districts, those responsible for health education use innovative approaches to reach their objectives, sometimes with measurable positive results. For example, several recent studies have shown reduced smoking among youngsters through the creative use of teenage peer counselors and the teaching of coping skills to help resist peer pressure.[49,50] Nonetheless, the formal socialization process at schools may not be powerful enough to overcome the informal socialization processes occurring simultaneously.

School physical education programs are another area of unrealized potential. Reductions in public school budgets have resulted in a decline in the quantity and quality of school physical education programs. Only one child in three now participates in a daily program of physical education, and in many areas the record is worse.[51] Coupled with the prevalence of after-school television viewing, this decline in physical education is a cause for concern. One of every six children taking a simple screening test for physical fitness designed by the President's Council on Physical Fitness and Sports currently fails the test.[52]

School-based health services, whether they involve the traditional school nurse or a full-service clinic, also offer the potential for teaching children about preventing illness and injury, self-care and the wise use of health services. Children are likely to have contact with a school nurse or health professional without the presence of their parents, and by about the third-grade level they are able to decide for themselves whether to report a personal illness.[53]

Schools can provide an important site for the development of personal health maintenance. School health promotion can take many forms: formal classroom education, supervised field experiences, peer education, education as part of the delivery of health services, physical education activities and teaching in conjunction with food services. Programs to promote good health-related habits through schools cannot hope to succeed without acknowledging the powerful influence of the school culture and adopting educational approaches that build upon its positive aspects.[48]

Training by Health Professionals

Illness Self-Help Programs

Unfortunately, there are very few studies of the role of health care providers, and physicians in particular, in shaping children's health-promoting behaviors. This is not to say health professionals are unimportant, but their place in the socialization process is not established. Health professionals do not generally use their time for health promotion.[6] Their orientation towards disease often hinders their playing a major role in facilitating overall personal health responsibility.

Nevertheless, health professionals have much clinical experience in influencing the development of childhood illness self-help and self-maintenance programs—that is, secondary prevention. In the treatment of children with chronic illnesses, physicians play a major role in helping children to take responsibility for their own health. Although chronic

illness self-help programs do not affect a large number of children, they do point out the capacity of children to be responsible for their own health and the positive influence of health professionals.

For this essay we will use asthma as our example, although we could have as easily used diabetes mellitus[54] or other chronic illnesses. A recent conference on self-management of childhood asthma[55] brought together representatives of a growing number of small clinical programs aimed at teaching children (and their parents) how to manage childhood asthma—the leading cause of chronic morbidity in childhood. Although each program was unique, they generally had certain features in common[56]: the development of patient responsibility, full disclosures of information pertaining to the illness, training in decision-making, the use of peer education and training of health professionals to encourage self-help attitudes and behaviors of their patients. These programs are aimed at 4- to 16-year-olds, who generally meet for five to eight weeks in small seminars, with role playing, homework and some parent participation. The health results seemed promising. Several of the studies, using random assignment to experimental and control groups, showed decreased emergency room usage, improved school attendance and better coping with asthmatic episodes.[57]

These asthma self-help programs emphasize some of the themes we have been developing in this essay: a full understanding of information pertinent to the illness and treatment (though none of the programs seemed to emphasize age-specific presentations of information), the development and training of health care self-responsibility (such as the Asthma Care Training for Kids from UCLA led by Lewis,[58] which emphasizes increased internal locus of control through the usage of the "you are in the driver seat" analogy of health and safely driving an automobile) and peer education as the most effective means of socializing behaviors.

The role of physicians in such programs was debated. Although some reservation about their training or appropriateness can be raised, physician presence seems important for compliance, to enhance program effectiveness and to maintain medical continuity for difficult asthma cases.[58] Several clinical and academic programs have emphasized that physicians can be trained to encourage self-sufficiency.[59,60] The asthma self-help programs show that physicians and other health professionals can be active participants in the development of a child's personal health maintenance.

Illness self-help programs show that children are capable when quite young of taking on responsibility for their own health, that specific areas of knowledge are and can be learned early in life and that health providers can play a major role in training for health responsibility. This topic strikes a positive note about children's ability to be responsible for their personal health maintenance.

Appropriate Health Care Usage Patterns

Lewis and Lewis[3,61] have established a major research effort to experimentally influence children's autonomy and responsibility for their own health care use. They have argued that to foster health promotion, health professionals must increase a child's own sense of control over health and move their practice away from the "you're in good hands" paternalism.[61] They initially focused on school nurses because there appears to be much social learning involving their use.[3,63] Data suggest that, as with adults, only a small percentage of students accounted for most use, even controlling for sickness,[3,63] and that such users were more dependent,[64] had lower self-esteem[62] and were more often girls.[64]

Lewis and Lewis designed and implemented a series of school-based interventions to test their theories that if children were encouraged to participate more in the decisions about health care usage, they would assume more responsibility for their health and would use health care resources more appropriately. Two stages of decision-making for children were studied. Whenever a child felt he or she needed to see a nurse, the child took a card from boxes located throughout the school, left the top portion on a teacher's desk and went directly to the nurse, with no permission from the teacher necessary. In the nurse's office, the child was examined and the findings presented and interpreted by the nurse. The nurse then asked the child to assist in formulating options for treatment and disposition, and subsequently to select one of the options. The nurse-child interaction concluded with the nurse asking the child, "The next time this happens, what do you think you can do about it?" Optimal choices were positively reinforced. Less than optimal choices were honored, but with feedback regarding the other available options the next time the problem occurred.

In the first study, one elementary school was examined. In the second replication study, four schools were allocated to different treatments—control; nurse practitioner; care cards plus nurse practitioner, and care cards, nurse practitioner and participation in decision-making. Children were tested before the intervention began and after two years on their health knowledge, health responsibility, health vulnerability and locus of control beliefs. In addition, the children's use of the school nurse was monitored.

In this free access system, children's patterns of usage of services were quite similar to those of adults. From 20% to 25% of the children never visited the school nurse during a period of two years; 8% to 12% of the children without serious medical problems made more than 50% of all visits. Use patterns seemed generally stable from one year to another and were consistent with parental, non-school health care use—that is, those children taken most often by mothers to physicians tended to be higher users of the school health nurse program.

In the first study, attitudes about health were enhanced. Children perceived themselves as less vulnerable, perceived their illnesses as less severe and had more positive attitudes about self-care, but no change in usage of health services was noted. In the second study, similar positive cognitive changes were noted, but, in contrast to the Lewis and Lewis theoretic expectations, free access led to increased use by some groups of students. Among the already high users of care, there was evidence of increased usage of and enhanced dependence on the health care services, rather than the promotion of a sense of self-reliance. It should be noted, however, that infrequent users of the school nursing programs decreased use in the free access situation. Sociodemographic differences in usage patterns were not affected. Health services usage behaviors appeared to be established early and were somewhat resistant to change.

Although the results were not supportive of their theories

on autonomy, Lewis and Lewis must be commended for initiating a line of experimental research on children's assumption of responsibility for their own health. Perhaps their limited health intervention was insufficient to balance out other simultaneous, less positive, health care use influences on the children's lives. Only by directly manipulating aspects of a child's sense of personal control over health can we begin to learn what will really influence them. Physicians' influential clinical positions could allow them to play a more thoughtful role in the setting up of clinic, hospital and private practice usage patterns. Dependency and self-sufficiency, in part, arise from structural characteristics of clinical practice.[65,66]

What Is to Be Done?

As noted in the beginning of this article, childhood is a critical time for assuming personal health responsibility, both as children and their future health as adults. After reviewing these five important factors influencing the development of personal health maintenance for children, what can be done to foster personal health responsibility for children? Although the research literature does not provide clear directions, certain generalizations can be drawn for practitioners:

- Respect the capacities of children to develop patterns for maintaining their own health. Children need the knowledge and skills with which to fulfill their potentials; health professionals can provide these without being patronizing or moralistic.
- Respect children's developmental levels. Children's abilities to understand the causes of illness change as they mature. As in sex education, questions should always be answered factually, but at the level of sophistication and interest of a child. Explanations should foster understanding and autonomy, not a sense of guilt and failure.
- The sensitivity of health professionals should be developed during their training. In working with children in the management of their own childhood illnesses and injuries, professionals can learn to recognize dependency and encourage autonomy.
- The capacity of parents to be role models and constructive shapers of their child's health behaviors merits greater attention. More health educational activities and literature for parents on the importance of early and regular encouragement of sound health habits are in order. The importance of health promotion for parents should be recognized as enhancing their capacities as role models.
- The power of television and the other media for shaping responsible personal health requires scrutiny. We need to learn how to lessen the impact of television as a negative influence on health behavior through its emphasis on programs of violence, drinking, smoking and drugs. Advertising directed toward children—especially concerning nutrition—needs much improvement. Certainly increasing the positive effects of television through more educational programming for children is an important goal for all who realize the value of wholesome child development for our society.
- Regular office visits for children and youth with health promotion as the focus should become commonplace, with appropriate time set aside for this purpose.
- Attention should be directed at providing financial support for health promotion and disease prevention services that can be offered through medical care services. The present health care reimbursement system tends to pay for curative services rather than for prevention.
- Enhancing the role of schools as a site for the growth of personal health responsibility is necessary. Efforts should continue to help schools develop health education as an integrated 12-year curriculum. Physical education programs can be made more useful for all children.
- Health education should emphasize that personal health maintenance is not exclusively a "life-style issue." As described in *Healthy People*,[1] health promotion and disease prevention are fostered by three categories: health services (key preventive services that can be delivered to individuals by health providers); health protection (measures that can be used by governmental and other agencies for groups or communities, as well as industry, to protect people from harm), and health promotion (activities that individual persons and communities can use to promote healthy life-styles). It is critical to note that all three categories must be involved in promoting health for children and that personal health responsibility is involved at all three levels. An exclusive focus on the life-style theme only would be in error.
- More research on the development of child health habits is needed. All five factors examined in this essay need further study. More experimental and longitudinal research, not just correlational research, is needed. The present inadequate knowledge base hinders the development of improved strategies for enhancing personal health maintenance.

The future of a society depends in considerable measure on the health of its children. Thus, personal health maintenance for children is an important issue not only for health professionals but for all citizens. Health professionals can learn to foster early patterns of personal health maintenance with increasing effectiveness, ultimately helping children to assume increasing responsibility with age. The building blocks for lifelong responsibility for personal health maintenance are laid down in childhood.

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Personal Health Maintenance for Adults

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The practice of adult medicine provides many opportunities to prolong life, prevent disease and disability and promote health. Essential steps in this process include establishing patient rapport, obtaining a comprehensive data base, providing periodic health examinations for both symptomatic and asymptomatic patients and helping patients change unhealthy behavior.

(Holbrook JH: Personal health maintenance for adults, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:824-831)

Individual health is determined by the interaction of factors such as heredity, the environment, personal behavior and medical care. Traditionally, physicians have been concerned with providing curative medical care. Currently, their role has expanded to include a range of activities intended to prolong life, prevent disease and disability and promote health. For example, while clinicians use coronary artery bypass graft procedures in the management of selected cases of coronary heart disease, they also seek to prevent atherosclerotic cardiovascular disease through risk factor reduction.

While acknowledging the crucial role played by governments and organizations in preventing disease and promoting health, this review focuses on the clinical services provided by physicians for individual adult patients.

Types of Preventive Care

Several levels of preventive care have been defined. Primary prevention refers to interventions that reduce the likelihood of disease occurrence. Immunizing with tetanus toxoid is an example of primary prevention. Secondary prevention refers to the detection and management of cases of asymptomatic, remediable disease. Identifying and treating an asymptomatic case of hypertension is an example of secondary prevention. Tertiary prevention refers to treating symptomatic patients with the goals of controlling disease progression, anticipating and avoiding complications and reducing functional impairment. The use of laser therapy for preserving visual acuity in patients with diabetic retinopathy is an example of tertiary prevention. In the actual practice of clinical medicine the distinction between levels of preventive care may become blurred. For example, the curative treatment of streptococcal pharyngitis with penicillin is also the primary prevention for rheumatic heart disease.

Health Promotion

In recent years both patients and physicians have shown an increased interest in personal health promotion. More than 85% of the respondents to a 1979 US health survey reported that they had "a great deal" or "some" control over their future health, and more than 65% of the respondents felt that they were doing an "excellent" or "good" job of taking care of their health.[1]

Most physicians surveyed in 1981 in Massachusetts stated that selected health-promoting behaviors were very important for the average person. However, in the same survey only 3% to 8% thought they were "very successful," whereas 40% to 57% reported that they were "somewhat successful" in helping patients change behavior.[2] A national physician survey found that internists ordered diagnostic tests and prescribed medication in 59% and 56% of patient encounters, respectively; in contrast, exercise or changes in diet (or both) were prescribed and patient counseling was recorded in only 9.8% and 19.4% of patient encounters, respectively.[3]

These data suggest that whereas physicians support the concept of health promotion, they may not take the time or feel confident to influence patient behavior.

Physicians' Role

Although many physicians spend a large part of their professional lives examining asymptomatic, apparently healthy persons, most practitioners have had little formal training in disease prevention and health promotion.[4] Standard textbooks of medicine include relatively little information on these subjects, but recently, authoritative guidelines have been issued for evaluating healthy persons.[5-7] Also, a new textbook of medicine includes a section on prevention for each of 664 topics; unfortunately, as noted by the authors, "there are many common and serious illnesses where prevention is not known, or is not accepted by all patients."[8] Studies also suggest that physicians are frequently not providing recommended preventive measures.[9]

Whether a patient sees a physician with a symptomatic problem or simply for a checkup, the initial visit often sets the tone for future interactions. The physician's genuine concern,

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TABLE 1.—*Preventing Nosocomial Complications*

Risk	*Complications*	*Preventive Invervention*
Bedfast	Deep venous thrombosis Decubitus ulcers	Low doses of heparin Excellent nursing care
Altered mental state	Falling Aspiration	Protective precautions—bed rails, patient positioning
Nutritional deficiencies	Specific syndromes Impaired immune system Poor wound healing	Recognition and treatment
Drug therapy	Adverse reaction—allergic reaction to penicillin	Appropriate precautions—elicit history, label chart
Diagnostic procedure	Untoward effect—postbiopsy bleeding	Appropriate precautions—check history and coagulation variables
Mechanical therapeutic procedure	Untoward effect—infected catheter	Appropriate precautions—sterile technique
Anesthesia and/or operation	Untoward effect—cardiac dysrhythmia	Appropriate precautions—preoperative evaluation
Severe medical illness	Psychiatric illness	Recognition and treatment
Admission to hospital	Nosocomial infection	Appropriate precautions—handwashing, isolation

ability to communicate and clinical excellence help build patient trust and confidence. A carefully elicited history, a skillfully done physical examination and appropriate laboratory tests and diagnostic procedures are essential for defining a patient's health status. Thereafter, the patient and physician can agree on programs to deal with symptomatic problems and to help maintain health. In asymptomatic patients, the discussion can proceed promptly to disease prevention and health promotion. As Relman suggests, physicians have an obligation "to get at the facts of disease prevention" and "to persuade patients to adopt those strategies that have been proven effective."[10] Accordingly, physicians should outline a health maintenance program to achieve optimal results.

As the patient's advocate and counselor, the physician may exert a decisive influence on patient commitment and concern for personal health maintenance. This influence may be enhanced if the physician emphasizes health maintenance during routine patient encounters and stresses the responsibility patients have for their own health. This influence may also be enhanced if the physician is a positive role model for a healthy life-style.

When a primary physician comprehensively manages a patient's medical care, directing and facilitating patient interactions with other physicians and health professionals, iatrogenic problems may be anticipated and avoided.[11] Physicians can also minimize iatrogenic disease by avoiding inappropriate therapy and unnecessary hospital admissions. Complications of appropriate treatment may be minimized by carefully monitoring a patient for both expected and unexpected untoward events such as drug side effects and interactions. A patient should understand why medication is prescribed and how long it should be taken. When admission to a hospital is indicated, the physician can systematically anticipate and help prevent nosocomial disease (Table 1). Adverse effects may be reduced by carefully assessing the benefit-risk ratio for planned tests and procedures. A physician should carefully monitor the cost of medical care and its impact on the patient's overall well-being. A patient with documented disease should understand the natural history of the disorder and how to adjust to it. Finally, the physician's concern for a patient should extend to the impact of illness on the patient's functional status at home, at work and in the community; physician support and involvement of other health professionals may minimize or prevent disabling psychosocial problems.

TABLE 2.—*Number of Deaths and Percent of Total Deaths for the Ten Leading Causes of Death—United States, 1981*†*

Rank	*Cause of Death‡*	*Number of Deaths*	*Percent of Total Deaths*
	All causes	1,977,981	100.0
1	Diseases of heart	753,884	38.1
	Ischemic heart disease	555,158	28.1
2	Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues	422,094	21.3
3	Cerebrovascular diseases	163,504	8.3
4	Accidents and adverse effects	100,704	5.1
	Motor vehicle accidents	51,385	2.6
	All other accidents and adverse effects	49,319	2.5
5	Chronic obstructive pulmonary diseases and allied conditions	58,832	3.0
6	Pneumonia and influenza	53,731	2.7
7	Diabetes mellitus	34,642	1.8
8	Chronic liver disease and cirrhosis	29,308	1.5
9	Atherosclerosis	28,004	1.4
10	Suicide	27,596	1.4

*Rates per 100,000 population.

†Modified from Monthly Vital Statistics Report, Vol 33, No. 3 (Suppl), June 22, 1984.

‡International Classification of Diseases, 9th revision, 1975.

Causes of Adult Morbidity and Mortality

Chronic diseases account for most of the 2 million deaths occurring annually in the United States.[12] About 60% of these deaths are due to ischemic heart disease, cancer and cerebrovascular disease (Table 2). Chronic diseases are also responsible for 60% of the days spent in acute care hospitals and for more than 50% of visits to physicians.[13] The profile of adult medical practice is strongly influenced by chronic diseases. Of the 20 leading problems or conditions encountered by internists in the United States, most are chronic (Table 3).[3] More than 60% of patient encounters with internists are return visits for disorders that require continuity of care.[3]

TABLE 3.—*Twenty Leading Internal Medicine Medical Problems/Diagnoses* *

Medical Problem/Diagnosis	*Percentage of Practice Encounters* †
Essential benign hypertension	6.8
Chronic ischemic heart disease	6.3
Diabetes mellitus	4.2
Medical or special examination	4.0
Acute myocardial infarction	3.3
Symptomatic heart disease	3.0
Acute URI—multiple or unspecified sites	2.0
Neuroses	2.0
Pneumonia, unspecified	1.9
Emphysema	1.8
Osteoarthritis and allied conditions	1.6
Acute, ill-defined cerebrovascular disease	1.3
Influenza, unqualified	1.1
Malignant neoplasm of breast	1.1
Symptoms referable to respiratory system	1.0
Asthma	0.9
Bronchitis, unqualified	0.9
Obesity, not specified of endocrine origin	0.8
Symptoms referable to abdomen and lower gastrointestinal tract	0.8
Acute bronchitis and bronchiolitis	0.8

URI = upper respiratory [tract] infection

*Reprinted with permission from the Robert Wood Foundation.[3]
†Seven additional diagnoses were required to attain a 50% level of practice encounters.

Chronic diseases have their roots in early life, develop asymptomatically and result in "accelerated loss of organ reserve."[14] Interest in preventing or diagnosing these disorders in an asymptomatic state stems in part from a better understanding of their natural history. When chronic disease becomes clinically apparent, the process may be catastrophic (such as with sudden cardiac death), not treatable (such as with lung cancer) or far advanced (such as alcoholic cirrhosis).

Risk Factors

Studies in persons who have chronic diseases have shown that certain risk factors occur more commonly in those with the disorders than in control groups. For example, a person who smokes and has hypertension and hypercholesterolemia is eight times more likely to have a coronary event than someone without these characteristics.[15] Reducing coronary heart disease risk factors in asymptomatic populations has a salutary effect on the likelihood of subsequent coronary events.[16] The death rate from coronary heart disease in the US declined by 25% between 1968 and 1978. This was most likely related to favorable changes that occurred in the coronary heart disease risk profile during the same interval in the US.[17]

The risk factor approach to health maintenance has become an essential clinical tool. In fact, some authorities equate risk factor reduction with primary prevention.[18] Data are collected through an interview, a physical examination and simple laboratory tests. The resulting patient portrait should be comprehensive because risk factors result from diverse influences—that is, they may be behavioral (driving without a seat belt), hereditary (glucose-6-phosphate dehydrogenase deficiency) or environmental (asbestos exposure); they may also result from more than one influence, such as with obesity. For educational purposes the risks may be presented to a patient as a quantitative profile. However, patients should understand that individual quantitative risk assessments are of limited predictive value.[19] Because of experience with risk factor modification, clinicians are collecting more data on life-styles and are becoming more involved in influencing patient behavior.

Life-styles

Breslow and colleagues found a positive correlation between several health habits and increased longevity.[20] These habits included not smoking, regular exercise, moderate or no use of alcohol and maintaining proper weight. Thus, these habits are the converse of well-recognized risk factors. A 1983 report from the Tecumseh Study, for the most part, corroborated these findings.[21]

The Surgeon General's 1979 report, *A Healthy People,* suggested that as much as 50% of US mortality is related to unhealthy behavior.[22] A recent commentary on that report stated that "at least 7 of the 10 leading causes of death could be substantially reduced if persons at risk improved 5 habits—diet, smoking, exercise, alcohol abuse, and use of antihypertensive medication."[23] In a 1980 Massachusetts survey, the frequency of respondents with unhealthy behavior was as follows: 43% were overweight, 33% smoked, 28% did not exercise and 12% had "robust" alcohol use.[24]

Physicians are in a key position to help change unhealthy behavior.[25,26] Patients receiving treatment for symptomatic disease should also receive instruction about personal behavior that has contributed to the disorder. Thereafter, the physician should explain the benefits of changing behavior and offer to assist the patient to achieve a more positive life-style. For example, a patient who has suffered an acute myocardial infarction is often receptive to the idea of quitting smoking. It may be enough for the physician to simply request that the patient quit smoking. If more assistance is needed, a more structured program can be used.[27] Also, nicotine-containing chewing gum may be a useful adjunct in smoking cessation programs.[28]

Defining Patients' Health Status

Effective physicians know their patients.[11] The history and physical examination constitute the foundation for understanding the patient and for generating a comprehensive data base. The latter consists of the essential information necessary for successful patient management. A comprehensive data base should be defined by individual physicians for specific patient populations.[8] The quality of the information gained from the history and the physical examination depends on the care and skill of the physician.

The comprehensive data base should be collected as promptly as possible. The interview may be facilitated by arranging for the patient to complete a questionnaire before the first visit.[8] Thereafter, during the interview, the physician can validate and amplify the data recorded in the questionnaire. A basic physical examination can be completed by an experienced physician in 10 to 15 minutes, if the patient has no major problems.[29] In Table 4 is an outline of such an examination, which consists of about 50 maneuvers. The results of the interview and the basic physical examination often lead to a more detailed physical examination and to specific laboratory tests.

The laboratory components of the comprehensive data base are defined by the physician according to individual patient requirements. For example, a 35-year-old woman requesting an initial "checkup" may require only a complete blood count, urinalysis, serum cholesterol level and Pap test; in contrast, a 50-year-old man with hypertension may require a complete blood count, urinalysis, automated chemistry panel (SMA-12), a fecal occult blood test (six specimens), an electrocardiogram and a chest film.

TABLE 4.—*Basic Physical Examination*

Minute	*Patient sitting*
1	Inspect general appearance Inspect hands, nails, skin, joints and palms Inspect and palpate arms; check range of motion of elbow, wrist and phalangeal joints Palpate, compare and count radial pulses
2	Measure blood pressure
3	Inspect face and head Test near vision Inspect conjunctiva and sclera Test pupillary reaction to light Instill phenylephrine hydrochloride (optional)
4	Examine ears, externally and with otoscope Inspect nose Inspect mouth and have patient phonate Test hearing
5	Test range of neck motion Have patient shrug shoulders and extend arms over head Palpate neck for nodes and thyroid
6	Observe chest symmetry with deep breath Percuss spine Percuss and auscultate lung fields
	Patient supine
7	Palpate breast and axillary nodes Inspect neck veins and palpate carotids Inspect and palpate precordium
8	Auscultate heart Auscultate carotids, midepigastrium and femoral areas
9	Inspect and palpate abdomen Palpate bimanually for liver and spleen Palpate inguinal nodes and femoral pulses
10	Inspect and palpate legs and flex joints Test for pretibial edema Palpate both dorsalis pedis pulses Test plantar flexion reflexes
	Patient sitting
11	Inspect breast for asymmetry, retraction (in women) Perform ophthalmoscopy
12	Test nervous system: wrinkle forehead, show teeth, protude tongue, test biceps, knee and ankle reflexes and extend arms
	Patient standing
13	Observe gait Examine male genitalia: Inspect and palpate penis, epididymis, testes and inguinal canals for hernia Perform rectal examination
	Patient supine
	Examine female genitalia: Inspect external genitalia Inspect vaginal vault with speculum Palpate vagina, cervix, uterus and ovaries Perform rectal examination

*Modified and reprinted with permission from Hillman RS, et al.[29 (p 102)]

Screening and the Periodic Health Examination

Successful screening programs focus on common conditions and diseases for which effective, early interventions are available. The periodic health examination (PHE) consists of a package of interventions designed to achieve these goals.

Although PHEs of asymptomatic patients have been a fixture on the American scene, their value has come under scrutiny. Proponents suggest that PHEs facilitate the early identification of risk factors, the early diagnosis of treatable diseases, improved management of known problems, promotion of healthy life-styles, economic savings, increased patient rapport and more timely access to medical care, and they result in decreased morbidity and mortality. Critics counter that PHEs lead to diagnoses for which no treatment is available, anxiety in patients appraised of asymptomatic problems, a false sense of security in patients when PHEs elicit no abnormalities and escalating medical costs, and they fail to reduce morbidity and mortality.

The only prospective clinical trial designed to study the periodic health examination was conducted among 10,000 members of the Kaiser-Permanente Health Plan.[30] The mortality for two "potentially postponable" diseases, hypertension and colorectal cancer, was significantly less in the group receiving regular PHEs compared with a matched control group. However, total mortality was similar in the two groups.

Several analyses of PHE data have been done, including those by Frame and Carlson,[31] Breslow and Somers,[32] the Institute of Medicine,[33] The Canadian Task Force on the Periodic Health Examination,[5,34,35] the American Cancer Society,[36] the American College of Physicians,[6] the Mayo Clinic,[37] the Henry Ford Hospital[38] and the American Medical Association.[7] Some of these reports are based on standardized assessments of data supporting specific maneuvers and interventions.[5,31] In many areas the data are inadequate to support scientifically valid recommendations. Thus, it is not surprising that there is a notable lack of agreement among experts on what the PHE should include and how frequently it should be done. Nonetheless, a consensus is developing that a clinician should streamline and target a PHE to meet individual patient needs. There is also general agreement that regular screening is indicated for hypertension and cancer of the breast, cervix and colon. Some experts do not recommend including a history and physical examination in the PHE[5]; apparently, this judgment is based solely on the efficacy of interventions to prevent specific diseases and unhealthy states.[39] There are additional important reasons for doing PHEs—obtaining new clinical data, teaching and counseling about personal health maintenance and enhancing patient rapport—which should be considered when determining its components.[25]

PHE Content and Scheduling

After a comprehensive data base is obtained, a periodic health examination should be scheduled at regular intervals for both asymptomatic patients and those with well-documented diseases. The PHE should consist of an interim interview, a basic physical examination and selected laboratory and other diagnostic studies. This interview differs from the initial interview used to establish the comprehensive data base. It is usually brief and emphasizes established problems,

common preventable disorders, life-styles and emotional status. The basic physical examination is a useful screening tool for hypertension and selected types of cancer—skin, oral, thyroid, breast, cervical, rectal, prostatic, testicular and lymphatic.

The laboratory and diagnostic components of the PHE should be accurate, safe and practical. The Pap test, mammogram, fecal occult blood test and serum cholesterol measurement meet these criteria and should be included in the PHE.

Pap tests have contributed to the decline in mortality from cervical cancer.[36] Women should have a Pap test at the time sexual activity begins and should have it repeated a year later. If these two initial tests are negative, it should be repeated at three-year intervals.[36] Women who are at high risk for cervical cancer should have a Pap test more frequently.

Mammography results in reduced breast cancer mortality in women older than 50 years.[40] It can detect clinically occult breast cancer. To achieve maximum screening potential, mammography should be combined with regular breast examinations by the patient and physician. Beginning at the age of 40, mammography should be done triennially; after the age of 50, it should be done annually.[40]

The stool occult blood test is useful in screening for colorectal cancer. It has a high predictive value for cancer and may detect tumors that are less invasive than those diagnosed clinically.[41–43] The impact of the stool occult blood test on mortality is currently being studied. Until more definitive data are available, asymptomatic patients older that 50 years should have an annual test in which six stool specimens are submitted.[42,43] Although the American Cancer Society recommends regular screening for colorectal cancer with a sigmoidoscopic examination, this intervention has not been widely adopted.[43,44]

Hypercholesterolemia is a major risk factor for coronary heart disease. Initial screening for hypercholesterolemia should begin at or before age 20 years.[32,45,46] Because most cases of hypercholesterolemia in the US are acquired and diet-dependent, screening should be repeated at least at ten-year intervals.[31,32] Determination of the high-density-lipoprotein-cholesterol level may provide additional predictive data.[47]

A primary physician should either become proficient in doing tonometry or should refer patients older than 40 to an ophthalmologist for regular measurement of the intraocular pressure.[48] Patients should also be encouraged to receive regular dental care.

The content of a PHE and how often it should be given are influenced by a patient's age and sex. Because health problems increase with age, the PHE should be given more frequently in older age groups. A recommended outline for both the content and the frequency of a PHE for established patients is given in Table 5. Patients should be reminded by telephone or written notice about the recommended PHE schedule.

A PHE for Symptomatic Patients

The practice of internal medicine is heavily weighted toward caring for patients with symptomatic diseases (Table 3).[3] A PHE (Table 5) is also important for these patients; usually it should be included as part of their symptom-oriented medical care. Many of these patients require laboratory and diagnostic studies for proper management of their symptomatic problems, in addition to those recommended for a PHE. This probably explains, in part, why the laboratory tests most frequently ordered by internists in the outpa-

TABLE 5.—*The Periodic Health Examination for Established Patients*

Age	*Approximate Intervals*					
Years	*1 Year*	*2 Years*	*3 Years*	*4 Years*	*5 Years*	*10 Years*
20-29		BP Weight	Pap test*	. . . . .	Basic PE†	Chol Td
30-39		BP Weight	Pap test	Basic PE†	. . . . .	Chol Td
40-49	BP Weight Breast exam Rectal exam	Tonometry	Basic PE† Mammogram Pap test	. . . . .	. . . . .	Chol Td
50-59	BP Weight Breast exam Rectal exam Stool guaiac‡ Mammogram	Basic PE† Tonometry	Pap test	. . . . .	. . . . .	Chol Td
60+	Basic PE† Stool guaiac‡ Mammogram Influenza vaccine Pneumococcal Polysaccharide vaccine (once)	Tonometry	Pap test	. . . . .	. . . . .	Chol Td

BP=blood pressure, PE=physical examination, Chol=Cholesterol level, Td=tetanus-diphtheria booster

*Three-year interval after two initial negative Pap tests at one-year interval.
†See Table 4 for components.
‡Six stool specimens.

tient setting (Table 6) are not among those recommended for screening of asymptomatic patients.[3]

Many of these symptomatic patients are in high-risk groups and require monitoring for tertiary prevention, such as patients with a prosthetic heart valve. Preventive monitoring may also be indicated for patients with asymptomatic inherited disorders (avoiding anesthesia in a patient with malignant hyperthermia), for patients with occupational exposures (uranium mining and lung cancer) and for patients who belong to specific socioeconomic groups.

TABLE 6.—*Ten Leading Diagnostic Procedures Ordered by Internists for Ambulatory Encounters* *

Diagnostic Procedure	*Percentage of Ambulatory Encounters*
Complete blood count, urine analysis	31.7
Electrocardiogram	16.4
Chest x-ray	15.9
Blood chemistry	15.7
"Panel"—automated	13.0
X-ray—other	6.2
Tests—other	6.1
Serology/VD	4.2
Pap smear	4.2
Culture	4.2

VD = veneral disease

*Reprinted with permission from The Robert Wood Foundation.[3]

Immunization

The effectiveness of immunization as a preventive measure is well-documented. Nonetheless, many patients have not received recommended immunizations.[49] Thus, physicians should routinely review each patient's immunization status including recommended vaccines for all adults, for those with unusual susceptibilities, for those with unusual exposures and for travelers (Table 7).[50,51]

Physicians should determine whether patients have been properly immunized in childhood against diphtheria, tetanus, measles, mumps and rubella.[52] Any deficiencies should be corrected. Immunity against tetanus and diphtheria should be maintained by giving a tetanus-diphtheria booster every ten years.[50] Adults older than 65 years should receive an annual trivalent influenza vaccination and a single pneumococcal polysaccharide vaccination.[53,54]

Patients who have unusual susceptibilities to specific infections should receive appropriate vaccinations, such as

TABLE 7.—*Commonly Used Active Immunizing Agents in Adults* *

Disease	*Preparation*	*Dosage Schedule*	*Comments*
Routine Use for All Adults			
Tetanus-diphtheria	Tetanus toxoid combined with diphtheria toxoid, adult type (Td); tetanus toxoid (T)	IM, at least every 10 years	Routine schedule plus management of wounds and management of contacts of cases of diphtheria; absorbed Td is preferred for all cases
Use in Selected Populations			
Elderly persons and persons with chronic disease			
Influenza	Influenza virus vaccine, trivalent	SC annually	Annual immunization of high-risk persons; those over 65 years of age and persons of any age with chronic disease; persons who provide essential community services
Pneumococcal disease	Pneumococcal polysaccharide vaccine	SC once	Immunization of high-risk persons over 2 years of age, and all persons over 65 years of age
Postexposure prophylaxis of animal bites			
Rabies	Human diploid-cell rabies vaccine	Five 1-ml doses	Pre-exposure prophylaxis only in special situations
Adolescent girls and women			
Rubella	Rubella virus vaccine, live	SC once	Adolescent girls and women who are unimmunized or who have no serum antibodies
Adolescent and young adults			
Measles	Measles vaccine, live	SC once	Adolescent and young adults who have not had measles and have no serum antibodies to measles, or who have not received previous live virus vaccine; postexposure protection
Mumps	Mumps virus vaccine, live	SC once	Prepubertal and adolescent boys who have not had mumps or mumps vaccine
Special groups			
Poliomyelitis	Poliovirus vaccine, live, oral trivalent (oral polio vaccine) Poliomyelitis vaccine (inactivated polio vaccine)	Three doses	Not for routine use; inactivated polio vaccine for primary immunization of special groups of adults; oral polio vaccine for booster in special situations (need for routine booster not established)
Meningococcal disease	Meningococcal polysaccharide vaccines	SC once	Only for special groups of persons at high risk
Hepatitis B	Hepatitis B virus vaccine	Three IM doses	Immunization of patients at increased risk: health care personnel; IV drug users; homosexuals; recipients of factor VIII and IX concentrates; sexual partners of HBsAg-positive patients

IM = intramuscularly, SC = subcutaneously, IV = intravenous, HBsAg = hepatitis B surface antigen

*Modified and reprinted with permission from American College of Physicians.[50]

TABLE 8.—*Long-term Medication Use and Disease Prevention*

Reduction in Frequency of Symptomatic Disease

Disease	*Treatment*
Migraine	β-Adrenergic blockers
Gout	Allopurinol, uricosurics
Nephrolithiasis	Thiazides, allopurinol
Manic-depressive psychosis	Lithium, antidepressants
Mediterranean fever	Colchicine

Reduction in Frequency of Complications

Risk Status	*Treatment*	*Complications*
Hypercholesterolemia	Cholestyramine	Coronary heart disease
Atrial fibrillation	Warfarin sodium	Embolic stroke
After coronary bypass graft operation	Aspirin, dipyridamole	Graft occlusion
Postmenopausal women	Estrogen, calcium	Osteoporosis and fractures
After acute myocardial infarction	β-Adrenergic blockers	Death

polyvalent pneumococcal vaccine for asplenic patients. Patients with unusual exposures may require active immunization (such as hepatitis B vaccine [Heptavax-B] for health care personnel) or passive immunization (human immune globulin for persons exposed to hepatitis A).

Chemoprophylaxis

Both short- and long-term chemoprophylaxis are effective in reducing the likelihood of contracting several infectious diseases. Antibiotic prophylaxis for selected surgical procedures can decrease the incidence of infection.[55] Antibiotic prophylaxis for bacterial endocarditis is a common practice, although the efficacy of this intervention has not been clearly documented.[56] In tuberculin-positive patients and in patients residing in areas endemic for malaria, long-term therapy with isoniazid and antimalarial medications is effective in preventing active tuberculosis and malaria, respectively.

Experience with the most common disorder seen by internists, hypertension, has proved the efficacy of long-term drug therapy for secondary and tertiary prevention; most appropriately treated hypertensive patients are asymptomatic and have a reduced risk of death and disability. In recent years the preventive use of long-term drug therapy for a variety of disorders has increased. Long-term medication use reduces the frequency of disease symptoms and complications (Table 8). The evidence supporting such an approach varies from strong to marginal.[57,58] Examples of this approach include the use of cholestyramine in patients with hypercholesterolemia to reduce the incidence of coronary heart disease and the use of β-adrenergic blockers to reduce the frequency of migraine headaches. Adjuvant chemotherapy is also given to selected cancer patients—such as certain premenopausal women with breast cancer—to enhance the likelihood of tumor-free survival.[59]

Recommendations

- Physicians should help close the gap between what is known about personal health maintenance and what is actually achieved, by taking advantage of practice opportunities to prevent disease and promote health.
- A comprehensive data base should be obtained on each patient. Thereafter, appropriate plans for primary, secondary and tertiary prevention and health promotion should be developed.
- After establishing a comprehensive data base, periodic health examinations should be scheduled for each symptomatic and asymptomatic patient. For the former, a PHE can usually be included as part of routine care. A PHE should consist of an interim interview, a basic physical examination and selected laboratory and other diagnostic studies. As patients age, a PHE should be given more frequently and should be more comprehensive.
- Physicians should increase their involvement and their skills in helping patients change unhealthy behavior. Specifically, they should assist with smoking cessation, help change harmful drug use and drinking patterns, prescribe "prudent" diets and help establish regular exercise programs.
- Physicians should review each patient's immunization status and correct deficiencies. All adults should receive the tetanus-diphtheria booster at ten-year intervals. All patients older than 65 years should receive an annual influenza vaccination and a single pneumococcal polysaccharide vaccination.
- Physicians should carefully monitor the aforementioned recommendations to ensure correct scheduling and to facilitate followup on abnormal results. Patient monitoring forms and computerized records help achieve these goals.[60]

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Preventive Health Care for the Elderly

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Demographic, economic and humanitarian considerations dictate that effective preventive health care be provided to the elderly. A disease-specific approach to geriatric preventive health care will not suffice; measures to enhance or maintain physical, mental and social function must also be emphasized. Unfortunately, the effectiveness of many preventive care procedures has not been adequately investigated in the elderly. Research is urgently needed to determine the efficacy of and appropriate target population for various geriatric preventive health care measures.

(Stults BM: Preventive health care for the elderly, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:832-845)

Elderly persons aged 65 years and older are the fastest growing segment of the population in the United States. Between 1960 and 1980 there was a 24% increase in the population younger than 65, but there was a 55% increase in the population 65 and older.[1] More important, there was a 100% increase in those aged 75 to 84 years and a 140% increase in the population older than 85.[1] These "old-old" persons 75 years and older are more likely to suffer from chronic illnesses and to require costly medical care than are younger persons. Although persons aged 65 and older compose only 11% of the US population, they consume 30% of the national health funds and 50% of the federal health budget.[2] By the year 2040, the elderly may consume 50% of the total health care dollars.[1] A small segment of the elderly population, perhaps a fourth of the total, is responsible for much of this expense. This segment is comprised of those elderly, most often the "old-old" (75 and older), who are either confined to an institution or are at high risk of being so placed because of chronic illness and disabilities.[2,3] Elderly persons now occupy 90% of nursing home beds,[2] and the elderly nursing home population is expected to double in size between 1980 and 1990.[4]

Currently, 30% of the practice of internists and medical subspecialists is devoted to the elderly,[4] and this may increase to 50% within the next 20 years.[5] Physicians should be aware that the life expectancy of elderly persons is surprisingly long. The average person aged 65 can expect to live another 15 years[5(pp17-34)] and remain functionally independent for ten of those years.[6] Persons aged 75 and 85 have average life expectancies of ten years and six years, respectively, and will remain functionally independent for about half that time.[5(pp17-34),6]

In view of the above considerations, providing preventive health care to the elderly must be a major concern of both primary care physicians and the health care system. Unfortunately, inadequate data are available to define what constitutes effective preventive health care for this segment of the population.[7-14] The preventive care measures that are useful and the frequency with which they should be applied have generally not been determined in scientifically adequate studies. Moreover, what constitutes necessary and effective preventive care procedures may vary considerably for relatively healthy elderly persons in a community compared with the "frail" elderly (those with serious functional disabilities) in a community, or compared with those elderly residing in institutions; future research must distinguish among these different subgroups. Controlled studies are needed to determine whether preventive health care programs can improve or maintain elderly patients' health, functional abilities, independence and life satisfaction and hopefully prevent, or at least prolong, the time before they require placement in an institution. The few preliminary studies of preventive care for geriatric outpatients have not shown definite benefit with respect to medical conditions and functional state, but they have noted that considerable expense and physician time would be required to initiate a preventive program for the elderly in both ambulatory and nursing home settings.[15-18]

Other obstacles may also hinder providing preventive health care to the elderly. Many elderly persons—nearly 90% by some estimates[7]—do not regularly visit a personal physician. This appears to be due to several factors: lack of finances or transportation, geographic and cultural barriers, apathy or a sense of futility concerning their own health, or a combination of all of these. Additionally, many elderly persons fail to report their illnesses and health needs until they reach an advanced stage of disease and disability when thera-

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ABBREVIATIONS USED IN TEXT

T_4 = thyroxine
Td = tetanus-diphtheria [toxoid]
TIG = tetanus immune globulin
TSH = thyrotropin [thyroid-stimulating hormone]

peutic interventions may be less effective.[2,9] The financing of health care for the elderly through medicare, medicaid and most third-party insurance carriers is geared to acute hospital and nursing home care rather than to preventive care. Preventive measures such as periodic health examinations, dental care, foot care, mental health services, eyeglasses, hearing aids, immunizations and many community health services are often inadequately funded.[2,19] How effectively elderly persons would participate in preventive health care programs is also not known. Of special concern is the apparent attitude or approach of physicians toward elderly patients. Although elderly patients have more health problems (medical and psychosocial), take more medication and are more likely to have significant communication difficulties than younger patients, physician-patient encounters are actually *shorter* for patients aged 65 and older than for those aged 45 to 64 years, especially for comprehensive and consultative visits.[20] Similarly, elderly patients average only one more physician visit per year than younger patients.[5] The causes of this physician-patient behavior and its relationship to the provision of preventive health care to the elderly have not been determined.

On the basis of the limited data now available, recommendations for potentially useful preventive care measures for the elderly have been made by several sources (Table 1).[7,11,12,21-23] Of particular importance is the recommendation that persons aged 65 through 74 be seen regularly every two years and those aged 75 and older be seen annually to assess the "progressive incapacity of aging"[12] that may occur with respect to physical, social and psychological functions.[12,23] The Canadian Task Force on the Periodic Health Examination recommends that this intervention be accomplished via a home visit by a physician.[12] It is important for primary care physicians to understand the patterns of health, disease and disability in elderly persons that have generated this recommendation for routine biennial or annual visits by (or to) their elderly patients.

Health Problems of the Elderly

Progressive decrements in physical, mental and social function may occur with advancing age. Multiple factors contribute to this decline (Figure 1). First, there is a physiologic age-related decline in organ function from the fourth through the ninth decades,[24-26] the magnitude of which varies considerably among different persons.[24] While these physiologic losses do not significantly compromise the overall function of an elderly person, in the event of a superimposed illness or injury they may result in more profound dysfunction and a longer recuperation time than in younger persons.[26,27] Physical and mental inactivity (disuse) may also compromise organ function with advancing age.[28,29] Some of the decline in organ function that has been attributed to physiologic aging may instead be due to disuse and therefore be preventable or reversible with appropriate therapy.[28] The prevalence of chronic physical and mental illness increases dramatically

TABLE 1.—*Potential Geriatric Preventive Health Measures*

Primary Prevention
Immunization
Influenza
Pneumococcus
Tetanus
Health promotion
Accident prevention
Physical fitness
Nutrition
Secondary Prevention—Early Detection and Treatment
Hypertension
Diastolic
Systolic (isolated)
Cancer
Breast
Colon
Cervix
Sensory deficits
Vision
Hearing
Mental health
Dementia
Depression
Alcoholism
Social support system
Iatrogenic disease: Drug therapy
Miscellaneous
Urinary incontinence
Podiatric disorders
Hypothyroidism
Tertiary Prevention—Rehabilitation
Comprehensive assessment of function: physical, psychological, social
Every 2 years for ages 65-74
Yearly for age 75 and older

with age, particularly in persons 75 and older.[2,5] The rates for chronic illnesses in the elderly such as arthritis, hypertension, organic heart disease, sensory impairments and urinary incontinence are about twice the rates in persons younger than 65.[5] Nearly 25% of community-dwelling elderly have symptomatic mental illness, including 10% with significant depression and 5% with dementia.[2] Potentially serious psychosocial stresses are common and include undesired retirement, inadequate finances, death of a spouse or the necessity of moving away from the family home. Many elderly persons will simultaneously suffer from several of these chronic physical or mental conditions.[2,9,13]

The magnitude of the decrements in physical, mental and social function varies tremendously among elderly persons. The vast majority of the elderly are able to tolerate and adjust to their functional impairments or disabilities and remain independent within the community.[2] However, a significant minority have major functional disability. Nearly 20% of the elderly aged 75 through 84 and 30% aged 85 and older are unable to carry on major activities such as leaving home, doing housework or cooking, compared with 7% with similar disability who are younger than 65.[2] Nearly 10% to 20% of persons aged 80 and older are unable to carry on even basic activities of daily living (bathing, dressing, eating, toileting) versus 4% younger than 65.[2] Because of this dependency many of these elderly persons will require placement in a nursing home unless adequate social support can be obtained from family, friends or the community. Whereas only 5% of

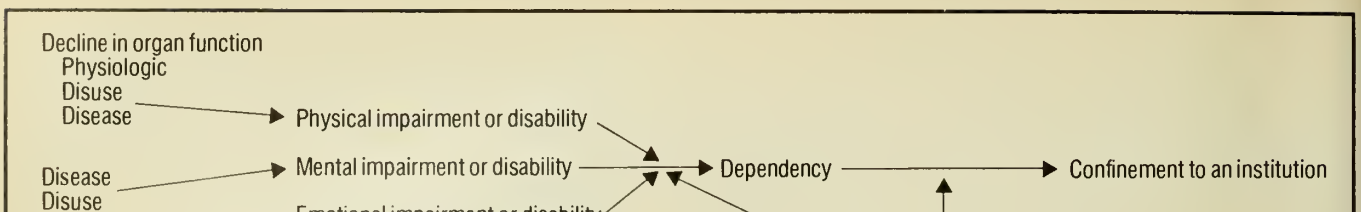

Figure 1. Loss of function and independence with age.

persons older than 65 years are in nursing homes, 20% older than 85 reside in them; the elderly have a 20% chance of requiring at least temporary nursing home placement at some time in their life.[2]

Unfortunately, much chronic illness and disability in elderly persons are unreported or undetected. A number of studies suggest that 40% to 50% of elderly patients' health problems are unknown to their personal physicians.[2,9,15,22,30] While cardiac, pulmonary and major central nervous system disorders were both reported and detected in most studies, disabilities such as urinary incontinence, locomotor dysfunction, defective hearing and vision, podiatric problems, depression, alcoholism and nonmedical social needs were not. Nearly half of these disorders were amenable to treatment. Left untreated, some of these problems may progress in severity and result in significant limitation of function and even dependency and confinement to an institution. The reasons these health problems are unreported or undetected are not known with certainty. Elderly persons may fail to report some medical conditions because they believe disease and disability are natural accompaniments of aging or that no effective therapy is available. They may fear placement in an institution if they bring up such problems. Others may be depressed and lack the desire to regain their health. Some may feel the health care system is unresponsive to their needs.[2,13,26,30] Physicians may fail to detect these problems due to inadequate training and a lack of awareness of the problems' existence or importance. Physician bias against preventive care for the elderly may also play a role.[20]

This high prevalence of physical, psychological and social dysfunction in elderly persons and its frequent failure to be reported or detected have led to the recommendation for routine comprehensive functional assessment of elderly patients either biennially or annually according to their age.[12,23] Because many illnesses of the elderly are chronic and incurable, a disease-specific approach to preventive health care that emphasizes only the primary prevention or early detection and treatment of disease will not, by itself, suffice.[31] Primary care physicians must also assess physical, psychological and social function. If deficits are found the physician must initiate treatment and rehabilitation to improve or maintain a person's condition or at least slow deterioration in function. In this way dependency and subsequent admission to an institution may be prevented or forestalled. When functional abilities cannot be restored, a physician should attempt to marshal an adequate social support system using family or community resources, or both, to maintain an elderly person in the community. Unfortunately, practical and clinically validated instruments by which a physician can assess physical and especially psychological and social function in the office or home are not yet available.[9] Ongoing research in the field will hopefully remedy this deficiency in the near future.[32] In the meantime, to comprehensively assess the elderly, physicians must rely on their own clinical judgment and the assistance of allied health personnel including social workers, psychologists and physical and occupational therapists. Whether such a comprehensive approach to elderly persons will improve their health status over a prolonged period of time must be determined in future research.

Preventive Health Measures for the Elderly

Preventive health measures of potential utility for the elderly are listed in Table 1. The list is derived from several sources,* and it omits some maneuvers such as routine screening for anemia and diabetes mellitus suggested by others.[33] The available scientific data and pertinent medical literature regarding each maneuver are reviewed briefly below. In many instances the data are either inadequate or contradictory and strong recommendations to include or exclude a maneuver are not possible.

Primary Prevention: Immunizations

Influenza vaccination. During epidemics of influenza A and B, the elderly population frequently shows excess mortality and admissions to hospital from primary influenza pneumonia, secondary bacterial pneumonia and exacerbations of chronic cardiopulmonary disease.[34] As many as 80% of influenza-related deaths and 30% of admissions to hospital occur in persons older than 65 years despite a lower incidence of infection than is found in younger age groups.[35] Those elderly persons with coexisting chronic cardiopulmonary or metabolic diseases are at greatest risk, particularly if they are in an institution.[34] Influenza outbreaks in nursing homes have attack rates as high as 60%, with case fatality ratios of 30% or more.[34] Healthy persons older than 65 are also at increased risk of admission to hospital during influenza epidemics, but the rate is threefold to fourfold lower than in those elderly with chronic disease.[36] There are widely divergent estimates of influenza vaccine efficacy in the elderly varying from 5% to 85% protection rates.[35] The vaccine is probably 60% to

*References 5(pp 299-302), 11, 12, 21-23.

70% effective in reducing mortality and admission to hospital in elderly persons when it is adequately matched to the epidemic virus strains of a given season.[37,38] Some studies, however, suggest the benefits are limited to those elderly with coexisting high-risk chronic diseases.[38] The Centers for Disease Control have therefore further subclassified the high-risk population according to greatest need for annual influenza vaccination as follows: (1) persons with significant chronic cardiopulmonary disease and those residing in nursing homes or other chronic care facilities, (2) medical personnel and (3) otherwise healthy persons older than 65 years and those with chronic metabolic diseases.[34]

Unfortunately, there are serious problems in carrying out annual influenza vaccination in the elderly. Physicians are currently vaccinating only 54% of their elderly patients who have serious chronic disease and only 33% of their otherwise healthy elderly patients.[39] Medicare at this time does not finance the cost of annual influenza vaccination. Some studies even suggest that elderly persons frequently refuse influenza vaccination when it is offered.[40] Further research is needed to improve the delivery of influenza vaccination to the elderly in office, institution and hospital settings (perhaps using allied health personnel) and to increase acceptance of the vaccine.[41] In the meantime, physicians should try to develop an organized program in their clinic to improve the vaccination rate. The use of amantadine hydrochloride for treatment and prophylaxis of influenza A in the elderly has recently been reviewed.[34]

Pneumococcal vaccination. Influenza and bacterial pneumonia are the fourth leading cause of death in persons aged 65 and older[42]; 25% of all cases of pneumonia are caused by *Streptococcus pneumoniae* (pneumococcus).[43] The incidence of pneumococcal pneumonia increases with age and is twofold greater in persons older than 60 years than in younger persons.[43] Mortality from pneumococcal disease (pneumonia, bacteremia and meningitis) also increases severalfold with age, but this appears to be due more to the presence of coexisting chronic diseases than to advanced age alone.[42,44] The degree of morbidity and mortality in otherwise healthy elderly persons has not been well quantified.

A 14-valent vaccine against the pneumococcus has been available since 1977; this was replaced by a more comprehensive vaccine containing 23 serotypes in 1983. The efficacy of the vaccine is well established in young, healthy populations at high risk of pneumococcal disease. However, randomized controlled trials of the vaccine in older outpatients and in persons in institutions did not show definite benefit, perhaps due to an inadequate sample size.[43,45] As a result, until recently most authorities suggested use of the pneumococcal vaccine in persons who had chronic cardiopulmonary, metabolic or immunosuppressive diseases, but noted a definitive recommendation could not be made with respect to the otherwise healthy elderly.[37,44,46,47] However, two studies using the case-control method have now suggested that the pneumococcal vaccine may have 60% to 70% efficacy in preventing systemic pneumococcal infections in both chronically ill and relatively healthy persons older than 60 years.[48,49] The Centers for Disease Control now recommend pneumococcal vaccination for all persons older than age 65.[43] Medicare will partially reimburse the cost of pneumococcal vaccination in both inpatients and outpatients. Only a single vaccination with the 23-valent vaccine is recommended at this time. It may be given simultaneously with the influenza vaccine. Unfortunately, as with influenza vaccine, only 45% of physicians are currently administering pneumococcal vaccine to their elderly patients.[50] Organized hospital and office-based programs are needed to improve this rate.

Tetanus vaccination. Although tetanus is an uncommon disease in the United States, it carries a 35% to 50% mortality and is preventable with appropriate immunization.[51] The highest incidence of tetanus is in the elderly in whom mortality reaches 80%.[42] In recent studies 50% to 70% of persons aged 60 years and older lacked protective serum levels of tetanus antitoxin compared with only 15% of persons younger than 40 years.[52-54] The likelihood of having protective antitoxin levels decreases progressively with advancing age.[54] This appears to be due to inadequate vaccination coverage because two doses of tetanus-diphtheria (Td) toxoid confer adequate antitoxin levels to almost all elderly persons.[53] More than a third of elderly persons have never received a tetanus immunization, as formal immunization programs were not available during their childhood.[54] However, even in settings in which there is regular access to medical care including free immunizations, such as with health maintenance organizations, persons older than 70 years are vaccinated against tetanus only 50% as frequently as younger patients aged 20 to 39.[55] Again, primary care physicians need to provide organized programs of immunization for their elderly patients. Additionally, because they are less likely to have been adequately immunized, older persons are more likely than younger to require tetanus immune globulin (TIG) for tetanus-prone wounds.[37] Recommendations for administering Td toxoid and TIG have been recently summarized.[56]

Accident Prevention

Injuries are the fifth leading cause of death in persons older than 65.[57] While the elderly have lower rates of injury than younger persons, they suffer greater mortality and morbidity; they have twice the death rate from injury and three times as many days of restricted activity and bed confinement as any other age group.[58] Of the deaths, 50% are due to falls, 25% are due to motor vehicle accidents (a third of which are pedestrian deaths) and 10% result from burns.[58]

The frequency of falls increases dramatically with age, being particularly prevalent in persons aged 75 and older.[58] A third of community-dwelling elderly persons and 10% to 25% of the elderly in institutions fall each year; two thirds of those who fall once will fall again.[59] The mortality and morbidity from these falls is considerable; 70% of deaths from falls occur in persons older than 65 years.[57] In all, 200,000 elderly Americans break a femur or hip each year; of these, 15% die from complications and many others suffer prolonged or permanent disability. Multiple falls may impair the mobility of an elderly person due to fear alone and are a risk factor for placement in an institution.[5(pp137-152)]

Strategies to prevent falls require identifying the specific pathogenetic factors that cause them.[59] The causes of falls in the elderly are often multiple and complex, however, and may be difficult to identify in an individual patient. Host factors, such as abnormalities of gait, strength, coordination, vision, cardiovascular function and the like, may interact in a complicated fashion with adverse environmental conditions—stairs,

TABLE 2.—*Potential Strategies to Prevent Falls**

Encourage physical activity within limits of function of patient
Reduce environmental hazards
Eliminate obstacles, such as loose rugs, from floor
Advise handrails and good lighting for bathroom and stairs
Identify and correct contributing medical factors
Sensory deficits (vision, hearing)
Musculoskeletal impairment or disability
Orthostatic hypotension
Teach adaptive behavior
Canes or walkers
Gait training
Slow rising
Low, broad heels on shoes
Identify cause of previous falls and correct

*Adapted from Kane et al,[5(pp137–152)] Rubenstein[57] and Hogue.[58]

TABLE 3.—*Physical Fitness Prescription Recommendations for the Elderly**

Patient education
Importance of exercise for older adults of both sexes
Regularly scheduled activity program as a lifetime commitment
Obtain history and do physical examination; use exercise performance tests as indicated
Prescribe exercise regimen within limits of function of a patient
Follow-up with an active interest in the patient's exercise practices
Qualified supervision of exercise when indicated

*Adapted from the American Medical Association's Council on Scientific Affairs[63] and Fuller.[64]

obstacles, poor lighting, loose rugs and so forth—to produce falls.[57,59] The efficacy of various interventions to prevent falls in elderly persons has not yet been validated in controlled trials. Several potentially useful preventive strategies are listed in Table 2.

Elderly persons have a higher rate of motor vehicle accidents than any age group except those aged 25 and younger.[58] Whether this is due primarily to errors in judgment and perception or is also related to underlying medical conditions is controversial[58]; further research is clearly needed. Elderly persons with impaired vision, mental illness, epilepsy or major impairment of neuromuscular function should be counseled about limiting their driving or repeating an actual driving test to document adequate skills. Of all pedestrian deaths, 20% occur in persons aged 65 and older, generally at intersections; these accidents are likely related to the slow rate of walking of the elderly.[58] Elderly persons should be counseled about this potential danger.

Elderly persons experience a disproportionate number of burn injuries, including scalds from tap water, contact burns and flame injuries.[58] Scalds from tap water in the bathing area are both common and preventable in the elderly. They should be encouraged to set their hot-water heaters at a maximum 50°C (120°F) (most are set at greater than 55°C [130°F]), which will also save them money in energy costs.[58]

Physical Fitness in the Elderly

Cross-sectional studies suggest that with advancing age there is a progressive decrease in maximal oxygen consumption (a measure of the cardiovascular response to the stress of exercise), muscle strength, endurance and coordination.[29,60] Along with these changes, there is a progressive increase in the incidence and prevalence of physical disability.[29,61] While most elderly persons maintain substantial physical ability, nearly 25% of those aged 75 to 84 are unable to climb stairs or walk half a mile.[61] Among clinically healthy 80-year-olds, almost no women and only 20% of men are able to walk fast enough to cross a street with a traffic light.[62] After 80 years of age, 10% to 20% of persons are unable to carry out the basic activities of daily living.[2] What portion of these decrements in physical function is due to true physiologic aging and what portion to physical inactivity or disease (or both) is not known. Longitudinal studies in progress may provide answers to these questions. There is evidence, however, that physical deconditioning may play some role in this decline of physical function with age. Many biologic changes attributed to aging are quite similar to the functional losses induced by prolonged inactivity.[28] Habitually active older persons show less of a decline in maximal oxygen consumption than their sedentary counterparts.[60] If loss of physical function with age is due to physical deconditioning, exercise programs for the elderly may prevent or restore some of the loss of function. This is of great importance because even a modest improvement in muscle strength, endurance and coordination may have a pronounced effect on the ability of an elderly person to leave home, complete housework or even carry on the basic activities of daily living.[62]

As summarized in recent reviews, a number of studies have shown improvements in physical and even mental function in the elderly through exercise programs.[29,63,64] Many of these studies, however, have considerable limitations including small sample size, study populations not representative of the general elderly population and inadequate randomization and control groups.[29] Given these limitations, the studies still show improvements in aerobic capacity, muscle strength, flexibility, range of motion and coordination in these elderly persons. Although not well quantitated, psychological benefits have also been reported including improved psychomotor reaction time, better relaxation and general elevation of mood and self-image.[29] Comprehensive rehabilitation programs in nursing home patients have even improved the performance of activities of daily living, though the specific contribution of physical exercise is difficult to quantitate.[65]

Specific recommendations for physical fitness prescriptions for the elderly have recently been published (Table 3).[29,63,64] Primary care physicians must carefully design and tailor the appropriate exercise program for each of their elderly patients.

Nutrition in the Elderly

This is a topic of controversy in geriatric medicine, in large part due to the limited availability of adequate scientific data. The major controversy concerns the prevalence of undernutrition in the elderly. Some reviews emphasize that calorie, vitamin and mineral deficiencies are widespread among the elderly, therefore justifying a detailed nutritional evaluation as part of the routine assessment of most or all elderly patients.[66] Other clinicians dispute this claim and state that there is, instead, a very low prevalence of nutritional deficiency in the elderly in industrialized Western societies, largely limited to the 10% to 15% of the elderly with chronic illness severe

enough to have them confined to an institution or to cause them to be housebound.[5(pp199-222),67] They note that there is little or no evidence that unrecognized dietary deficiency causes disease or disability in the elderly, or that better nutrition for the average elderly person reduces or prevents morbidity.[5(pp199-222),67] They suggest that detailed nutritional assessment and preventive programs be concentrated on the minority of elderly persons at high risk of serious nutritional deficiency: those elderly persons with severe, chronic illness, especially if rendered housebound or confined to an institution; those with depression or social isolation (or both); those with severe dental and periodontal disease, and those of low socioeconomic status.[5(pp199-222),67] Historical evaluation of these high-risk patients should include information about access to food (transportation and finances), motivation and ability to prepare adequate meals and ability to consume them (dentition, appetite, dysphagia). Consultation with a dietitian may be invaluable. Physical examination provides only a gross estimate of nutritional status, and anthropometric measurements are not well standardized in the elderly population.[66] Measurements of serum albumin level, total lymphocyte count and skin test reactivity may provide useful information. For those elderly persons found to be undernourished, there are practical recommendations that may improve their nutrition.[66]

Obesity is more common in the elderly than is undernutrition, particularly among women; 20% to 25% of women aged 75 to 85 are obese.[5(pp199-222)] The importance of obesity as an independent risk factor for both total mortalityand cardiovascular mortality[69] tends to decrease with age. It is not clear how aggressively physicians should pursue a weight loss program for their obese patients, particularly those less than 20% to 30% above ideal body weight.[70] Certainly a weight loss program is indicated for those elderly patients who are grossly obese (40% or more above ideal body weight) or who are suffering complications from their obesity.

Secondary Prevention—Early Detection and Treatment

Hypertension, diastolic. About 15% of whites and 30% of blacks aged 65 years and older have diastolic hypertension as defined by a diastolic pressure of 95 mm of mercury or greater.[71] Most of these patients had the onset of their hypertension before age 65. Diastolic hypertension in the elderly carries the same relative risk and a greater absolute risk of cardiovascular morbidity and mortality than in younger persons.[72] Effective antihypertensive therapy appears to reduce the cardiovascular sequelae of diastolic hypertension in patients up to age 69,[73,74] but adequate studies are not yet available for patients aged 70 years and older.[75] There is an ongoing, randomized, double-blind multicenter study in Europe designed to answer this specific question (European Working Party on Hypertension in the Elderly) and results should be available in the near future.[76] Most authorities recommend treatment of elderly persons who have persistent elevations of diastolic pressure above 90 to 95 mm of mercury.[75,77] Because the lability of blood pressure increases with age, it is especially important in the elderly to confirm the diagnosis of diastolic hypertension with multiple blood pressure measurements over time.[72,76] Nonpharmacologic therapy (salt restriction, weight reduction and exercise) should be used initially, although its efficacy has not been determined. Low doses of diuretics and adrenergic inhibitor medications (methyldopa, clonidine hydrocholoride) have been shown to be effective and well-tolerated antihypertensive agents in the elderly[76] when nonpharmacologic maneuvers fail. Elderly persons should be monitored for adverse effects of the medications, particularly postural hypotension.

Isolated systolic hypertension. In economically developed societies systolic blood pressure increases linearly with age.[72] This is primarily due to decreased elasticity of the great arterial vessels from arteriosclerosis.[72] As a result, isolated systolic hypertension (usually defined as a systolic blood pressure above 160 mm of mercury with a diastolic pressure of less than 90 to 95 mm of mercury) is common in the elderly and more prevalent than diastolic hypertension in persons older than 70 years.[78] In all, 10% to 15% of persons aged 65 and older and 25% to 30% aged 75 and older have isolated systolic hypertension.[79-81] Even in the absence of other risk factors, systolic hypertension increases cardiovascular morbidity and mortality (stroke, congestive heart failure) twofold to threefold, the magnitude of the risk increasing progressively with the systolic pressure.[72,81] Evidence is not currently available as to whether treatment of isolated systolic hypertension in the elderly will reduce these cardiovascular complications. However, a randomized trial to answer this question is currently under way, sponsored by the National Institutes of Health.[77] In the meantime, several authorities suggest cautious treatment when the systolic pressure is persistently greater than 180 mm of mercury on multiple measurements, or greater than 160 mm of mercury in the setting of significant end-organ disease.[75,77,78,82] Maintenance of a systolic pressure in the range of 140 to 160 mm of mercury is a reasonable therapeutic goal. Nonpharmacologic therapy should be used initially. If ineffective, pharmacologic therapy with low doses of diuretics and adrenergic inhibitors appears to be both effective and well-tolerated, though patients should be monitored carefully for side effects, especially postural hypotension.[76,77,83]

Cancer Screening

Recent monographs are available that thoroughly review the current status of cancer screening in the elderly.[84-86] The elderly are at an exceptionally high risk for the development of cancer. While the risk of cancer developing is 2% between ages 20 and 50, it is 20% between ages 65 and 85[87]; 50% of all cancers and 60% of all cancer deaths occur in the 11% of the population that is older than age 65.[84(pp5-15)] The major sources of cancer deaths in men older than 65 are lung, prostate and colorectum, and, in elderly women, colorectum, breast and lung.[84(pp5-15)]

Despite this dramatic increase in incidence with age, very little is currently known about cancer in the elderly.[84(pp5-15)] What benefits can be expected in the elderly from primary prevention activities like cessation of smoking? How much benefit can be expected from early detection and screening programs in the elderly? While early detection and treatment through screening have been suggested to provide potential survival benefit for cancers of the cervix, breast and colorectum,[88] the elderly population has been generally omitted or underrepresented in most of the pertinent studies.[84(pp5-15)] Will the "young-old," aged 65 to 74, and the "old-old,"

aged 75 and older, both benefit in terms of survival or quality of life from cancer detection programs? How much toxicity might each of these groups suffer from the necessary diagnostic procedures? What about the elderly who are in institutions? There are also grossly inadequate data concerning the behavior of both elderly persons and their physicians with respect to the use of both primary and secondary cancer prevention activities. Some studies suggest that elderly persons receive less cancer screening than their younger counterparts.[86,89] In one investigation, 50% of women aged 75 and older reported that they had never been screened for cancer as compared with figures of 33% of women aged 65 and older and 20% of women younger than 65.[89] In the same study age was inversely related to the receipt of annual breast examinations and instruction in breast self-examination. There is also evidence that older age correlates with nonparticipation of women in a variety of cancer screening activities.[86] Finally, the elderly appear to be undereducated as to cancer risk, as 70% are unaware that the risk of cancer increases with age.[86] This is of great concern, especially in view of the previously described tendency of the elderly to fail to report their symptoms.

Breast cancer. Of all breast cancers, 50% occur in women older than age 65, with both the incidence and mortality increasing progressively with age.[90] There is no difference in the extent of tumor at the time of diagnosis in the elderly as compared with younger patients.[91] As a result, 5- and 10-year absolute postoperative survival rates following mastectomy are as good in patients older than 70 years as in younger patients.[92] The frequency of estrogen-receptor-positive breast cancers increases with age, so that elderly women are more likely than younger women to respond to hormonal manipulation.[90] Elderly women also respond to and tolerate chemotherapy for breast cancer as well as younger women, providing appropriate alterations in dose are made.[91] With respect to early diagnosis, the breast of an elderly patient may be easier to evaluate both by physical examination and by mammography.[93] Recent studies have indeed suggested that the benefits from regular breast cancer screening are greater with increasing age, although very elderly women were not examined in large numbers.[94]

All of these considerations argue for a vigorous approach to breast cancer screening in most elderly women. However, a recent study found that only 40% of women aged 75 and older were receiving annual breast examination by their physicians compared with 75% younger than 65.[89] Two thirds of women younger than 65 years but only a third older than 65 were instructed in breast self-examination. In a large radiology practice only 16% of mammograms done were in women older than 65 years and, of these, only a third were done as a routine screening procedure.[95]

The available evidence suggests that primary care physicians should place greater emphasis on instructing elderly women to do monthly breast self-examination and to undergo examination by their physician every year and mammography every one[88] or two[95] years.

Colorectal cancer. The incidence of colorectal cancer rises with age, peaking at about age 80; overall, 60% of colorectal cancers occur in persons older than age 65.[96] Once diagnosed and treated, the five-year survival rates for colon cancer are the same for patients aged 65 and 75 and older as for younger patients.[96] When patients older than 40 are considered, there is suggestive, though not definitive, evidence that annual fecal occult blood testing and proctosigmoidoscopy every three years (after two negative examinations one year apart) result in the detection of colorectal cancer at an earlier and more curable stage.[97] Together these considerations suggest that screening for colorectal cancer may be a useful preventive measure in elderly persons. However, only limited data are available to answer this question.[98,99]

In studies of fecal occult blood testing at the Memorial Sloan-Kettering Cancer Center (New York), only 8% of the study population (1,700 persons) was older than 70 years.[98] The incidence of heme-positive fecal smears increased progressively with age from 1.7% in the 40- to 49-year age group to 4.4% in the over-70 age group. Among the patients older than 70 who had positive smears, 23% proved to have colorectal cancer and 37% had adenomas. The compliance of the elderly patients with the necessary screening and diagnostic procedures was excellent, the Dukes's staging of their cancers was more favorable than in younger patients and there did not appear to be excess morbidity from the diagnostic procedures.[98] This was a highly select elderly population, however, who had voluntarily sought preventive medical care, and these results may not be generalizable to the entire elderly population. For example, in a recent study of the use of fecal occult blood testing in a nursing home, less than 10% of positive smears were caused by either colorectal cancer or adenomas; most lesions emanated from a duodenal ulcer or a cause could not be determined.[99]

Despite the promising preliminary studies noted above, at this time many questions remain unanswered concerning the final use of annual fecal occult blood testing and frequent proctosigmoidoscopy in the elderly population.[98] It is not known whether such testing will improve survival or quality of life, or both, whether all elderly persons should be screened or whether there will be too many false-positive tests and excessive morbidity from the necessary diagnostic procedures. Pending further information, primary care physicians will have to individualize their approach to each elderly patient.

Cervical cancer. Because the incidence of carcinoma in situ of the uterine cervix is extremely low after age 65, it is currently recommended that women older than 65 who have had repeated normal Papanicolaou smears without significant atypia be dropped from routine screening programs for squamous cell carcinoma of the cervix.[88,100] However, primary care physicians should be aware that 15% of women aged 65 to 74 years and 38% of women 75 years and older report never having had a Pap smear.[89] Because 25% of the cervical cancer incidence (excluding carcinoma in situ) and 41% of cervical cancer deaths occur in the population older than 65 years,[89] women older than age 65 without previous Pap smears should probably have periodic smears every one to three years for an indefinite period of time.

Early Detection of Sensory Deficits in the Elderly

Vision. The incidence and prevalence of defective vision and blindness increase sharply with age.[101] In all, 5% of persons aged 65 and older have severe visual impairments (inability to read normal newspaper print with conventional glasses), 1% are legally blind (corrected acuity less than 20/

200) and many more have less severe but still significant visual impairment.[102] In nursing homes, 50% of the residents have trouble seeing and 15% are severely disabled or are unable to see.[102] These numbers likely underestimate the true prevalence of severe visual impairment in the elderly, which is expected to double over the next 20 years.[102,103] Defective vision significantly decreases the mobility, safety and life satisfaction of elderly persons and ultimately can result in a loss of independence.[107] The disorders most often responsible for serious visual deficits in the elderly—cataracts, senile macular degeneration, glaucoma and diabetes mellitus—are each at least partly remediable with early detection and treatment, with the possible exception of senile macular degeneration.[101] Glasses and other optical aids will benefit many of the patients, as will rehabilitation programs that include environmental structuring and navigational skills.[102]

Unfortunately, it is estimated that only a few percent of the visually impaired elderly people in this country receive adequate vision services.[102] This may relate, in part, to the tendency of many elderly patients or their physicians to attribute visual loss to normal aging with a resultant low rate of referral to specialists and a large residual pool of preventable dysfunction. Primary care physicians should do routine screening for visual deficits in their elderly patients every one to two years. Visual acuity should be tested with a Snellen acuity chart and by asking a patient to read newsprint. An ophthalmoscopic examination should be done, but with a clear understanding of the low sensitivity and specificity of the examination as done by internists for detecting both glaucoma and diabetic retinopathy.[104] The utility of handheld tonometry to measure intraocular tension as a screening maneuver for glaucoma is controversial.[12,105] The Canadian Task Force on the Periodic Health Examination does not recommend it, believing there are too many false-positive results for it to be useful.[12] An alternative approach would be a regular referral (every one to three years) to community screening programs that use the more accurate applanation equipment.[5(pp223-233)]

The discovery of significant visual dysfunction is an indication for ophthalmologic consultation. When severe visual deficits cannot be adequately corrected, it may be useful to refer an elderly patient to community services for the visually handicapped. Finally, primary care physicians must consider the functional consequences of an elderly patient's visual deficits—that is, safety in the home, driving and avocational activities. This assessment may require a home visit by the physician or by an allied health worker.[102]

Hearing. The prevalence of hearing impairment in the elderly varies from 30% to 60% in different investigations according to the particular criteria used, the type of testing done and the characteristics of the elderly population being studied.[106] Hearing loss severe enough to produce disability may be present in 25% of persons aged 65 and older and 50% of persons older than 85 years.[107] Of patients in nursing homes, 30% to 50% have moderate to profound hearing loss.[106,108] Considerable morbidity may be associated with significant hearing loss.[106] Anger and frustration in these patients may result in withdrawal and social isolation. The incidence of depression may be twofold greater in elderly persons with hearing disability than in those with normal hearing.[109] Hearing disability may exacerbate confusion and paranoia in persons with dementia or psychiatric disease.[110]

Medical and surgical therapy is rarely able to correct hearing disability in the elderly. However, aural rehabilitation using hearing aids, education of the patients and family in communication techniques and structuring of the environment may significantly benefit many of these elderly persons.[106] Even in nursing homes where the high prevalence of mental incapacity may limit the therapeutic response, 15% of the hearing impaired may benefit from a rehabilitation program.[108]

The prevalence of hearing disability in the elderly, the associated morbidity and the potential response to rehabilitation programs all argue for the screening and detection of hearing impairment in the elderly.[12] In studies from both the community and nursing homes, however, self-reporting of hearing impairment by the elderly and detection by their primary care physicians were both found to underestimate the prevalence of hearing impairment by 50% or more, when compared with formal audiometric testing.[108,109,111] This discrepancy may be due to a variety of factors: a refusal to admit to hearing loss, failure to recognize hearing loss due to its gradual onset and slow progression or to coexisting cognitive deficits (such as dementia) and the belief of elderly patients or their physicians that beneficial therapy for hearing impairment is not available.[108] As a result, many elderly persons with potentially remediable hearing disorders may go without appropriate diagnosis and rehabilitation.

Primary care physicians should carefully screen their elderly patients annually or biennially for hearing deficits, using history and physical examination. The limitations of these maneuvers should be recognized, however, and audiologic or otolaryngologic consultation should be promptly requested for all suggestive cases. Additionally, consideration should be given to the recent proposal that all nursing home patients undergo routine audiometry.[108]

Preventive Aspects of Mental Health Care in the Elderly

Dementia. The prevalence of dementia in those older than 65 years is estimated at 5% to 20%.[112] Dementia is the most common reason for admission of elderly persons to nursing homes and is therefore a major expense to the health care system.[113] More important, dementia is a source of enormous personal suffering both to the patient and to the patient's family and friends.[114] Unfortunately, more than 70% of dementia cases in the elderly are due to Alzheimer's disease.[112] Primary prevention of this disorder is not possible, nor is beneficial treatment available following early detection (secondary prevention). Physicians frequently attempt to diagnose a cause of "reversible" dementia that may be present in 15% of demented elderly patients (usually drug toxicity or hypothyroidism).[112] Unfortunately, once the diagnostic evaluation is completed, many physicians abandon patients who have chronic dementia as untreatable.[115] This ignores the concept of tertiary prevention, whereby a physician attempts to maximize function and minimize disability and thereby slow the progression toward dependency and confinement in an institution. Such tertiary prevention can be of tremendous benefit both to demented patients and their care-givers. In a recent study of elderly outpatients referred for evaluation of chronic dementia, nearly half of these patients had previously unrecognized but treatable medical and psychiatric disease including depression, urinary tract infections, congestive

heart failure, Parkinson's disease, drug toxicity and a number of others.[112] Therapy for these disorders resulted in objective improvement in 25% of the patients. Careful assessment of a demented elderly patient's family and environment may also disclose unreported social and psychological needs amenable to intervention by other members of the health care team, such as social workers, home health aids and so forth.[112] These interventions may improve the function of both patient and care-givers enough to prevent or delay placement in an institution.

Depression. It is estimated that 13% of persons aged 65 and older have clinically significant depression warranting intervention, including 5% to 10% of community-dwelling elderly and 30% of elderly in nursing homes.[5(pp83-106),116] In men older than 80 years, the prevalence of depression may be as high as 24%.[116] The rate of suicide increases sharply with age in men: elderly men have a suicide rate threefold to fourfold greater than the rest of the population.[5(pp83-106)] Effective therapy (pharmacologic, electroconvulsive and psychotherapy) is available for elderly patients who have depression.[117,118] Despite the high prevalence of depression and the availability of effective therapy, however, elderly depressed patients are both underdiagnosed and underserved. It is common for physicians to miss a diagnosis of depression in the elderly[119] and, in one series, nearly 75% of cases of depression in elderly outpatients were unknown to the primary care physician.[111] Less than 5% of the clients of community health centers are aged 65 and older and less than 3% of the visits to office-based psychiatrists are by patients older than 65.[116] Only 30% of nursing homes offer mental health counseling as a routine service.[116]

Physicians may fail to make a diagnosis of depression in elderly patients for several reasons.[119] Physical illness is an important contributing cause of depression in the elderly,[116] and physicians may be too involved with a patient's physical disease processes to notice coexisting depression. Depression may also present in an atypical fashion in elderly patients—so-called masked depression, with pronounced somatic symptoms and an absence of classic psychiatric symptoms.[119] Finally, some psychiatrists and primary care physicians may be less interested in the mental health of their elderly patients as compared with their younger patients.[120]

Primary care physicians should carefully screen their elderly patients for signs and symptoms of depression, so that referral and therapeutic interventions can be initiated early. Risk factors include coexisting physical illness, recent bereavement, alcohol abuse and, perhaps, social isolation.[116] Elderly patients who have multiple somatic symptoms that remain unexplained after a thorough medical examination may be suffering from depression and need further investigation.

Alcoholism. The definition of alcoholism in the elderly is difficult but essentially includes excessive, persistent drinking that interferes with a persons's health and interpersonal relations.[121] There are no adequate large-scale studies of the incidence and prevalence of alcoholism in community-dwelling elderly persons.[122] Estimates of prevalence from available studies range from 1% to 23%, with an average of about 10% in persons older than 65.[121,122] Due to the greater difficulty in diagnosing alcoholism in elderly persons, this figure may be an underestimate.[122] Although the prevalence of alcoholism in the elderly is less than in younger persons,[121] it constitutes a serious public health problem. Alcoholism in the elderly may be a major etiologic factor in 15% to 20% of nursing home admissions, 10% of hospital admissions for acute conditions and 5% to 15% of medical outpatient visits.[121] There is evidence from studies in animals that an elderly person's brain may be more sensitive to both the acute and chronic effects of alcohol.[123] As a result, alcohol in amounts tolerated by younger persons may acutely impair the coordination and equilibrium of elderly persons and may be an important etiologic factor in falls and motor vehicle accidents, though this has not yet been confirmed. Chronic alcohol consumption may increase vulnerability to Alzheimer's dementia and reversibly exacerbate confusion in demented elderly persons. Alcoholism may interact with depression in the elderly in a vicious cycle and contribute to the high suicide rate in this age group.[124]

A disproportionately small number of elderly persons with alcoholism receive therapy for it, despite the fact that treatment may be nearly twice as effective as in younger patients.[122] This may in part reflect underdiagnosis of alcoholism in the elderly by primary care physicians. Two types of elderly persons with alcoholism have been identified.[122] Two thirds have had alcoholism all their lives but have survived into old age; diagnosis in this group usually is not difficult. The other third have the onset of the disorder in old age, perhaps partly in response to the psychosocial stresses of old age. These elderly patients are often not identified as having alcoholism as they do not manifest the classic social problems seen in younger persons with the disorder.[121,124] Elderly persons are more often widowed and retired and drive less frequently than younger persons, and so their alcoholism presents less frequently with marital stress, poor job performance or encounters with law enforcement agencies. Because many physicians are unaware of the relatively high prevalence of alcoholism among the elderly, they are unlikely to attribute nonspecific symptoms and signs or other health problems to alcohol abuse.

In view of the prevalence and morbidity of alcoholism in the elderly and considering its difficult diagnosis and relatively favorable response to therapy, primary care physicians should carefully screen the drinking habits of their elderly patients. High-risk elderly patients who are socially isolated, depressed or apparently demented, or who have recently suffered a fall or motor vehicle accident, should be evaluated carefully for alcoholism.

Social Support System

To live independently within a community, a person or couple must be able to adequately carry out certain social tasks such as housekeeping, transportation, food preparation, grocery shopping and social interaction with other people.[125] Failure to accomplish these tasks increases dependency and may result in being admitted to an institution.[5] Although the prevalence of social disability does increase with age, more than 90% of community-dwelling persons older than age 65 have minimal social disability and do not require extensive support.[125] Even in the "old-old" older than 75, only about 10% to 15% have major unmet social needs.[125] Social isolation among community-dwelling elderly persons does not increase much with age, and these elderly persons have as many

social contacts among relatives and friends as younger persons.[126]

Primary care physicians must attempt to identify the small subgroup of elderly with unmet social needs that place them at serious risk of institutional placement. Practical tools to effectively accomplish this are not yet available, though it appears that those elderly with significant physical and mental disability are at greatest risk, particularly if they are poor and without close family or friends.[5,7,126] Once identified, it is the responsibility of a primary care physician to marshal the appropriate family and community resources to provide for these unmet social needs. Families currently provide 80% or more of the home health care of the elderly in the United States, and nearly a third of nursing home referrals are the result of a breakdown of the family support system. Physicians may have to provide temporary or part-time relief for some families in the form of community services such as home nurses, home health aides and Meals-on-Wheels.[5] They must provide these services at the correct time. If they are given too early, scarce community finances are wasted. If the services are given too late, the patient may need to be permanently confined to an institution. Ideally, physicians should be aware of the variety of support services available in their community, which of their patients qualify for these services and how to arrange for them. In practice this is a complicated maze in which it is difficult to match the specific needs of individual elderly patients with the services for which they qualify.[5(pp303-320)] The assistance of a knowledgeable social worker may be of great value. Preliminary studies suggest that with appropriate use of family and community resources, most elderly patients referred for skilled and unskilled nursing home placement may remain in the community.[7] Maintaining an elderly patient's social support system may therefore be a most important preventive health maneuver.

Iatrogenic Disease: Drug Therapy

Elderly persons receive more drugs, including a greater number of potentially toxic drugs with a narrow therapeutic ratio, than do younger persons.[127-129] In all, 80% to 90% of elderly persons living in the community take some medication regularly, and 15% receive four or more drugs a day; two thirds of these medications are by prescription and a third are obtained over the counter.[127,129] The most common prescription medication in outpatients includes diuretics, digoxin, antihypertensives, antiarthritis medications and anxiolytics.[127,128,130] Drug use is even more extensive in nursing homes with the average patient receiving three to four prescription drugs per day, primarily psychotropic drugs, digoxin and antihypertensives.[127,128]

Adverse drug reactions and their associated morbidity and mortality also increase with age and are twice as frequent in persons older than 65 years as in the younger population.[129,131] The drugs most often at fault are those most frequently prescribed and include cardiovascular medications, hypnotics, anxiolytics, antidepressants and anti-Parkinsonian drugs.[128,129,131] Unfortunately, elderly persons are only half as likely as younger persons to report adverse symptoms from drugs to their physicians[132]—another manifestation of their tendency not to report illness. Multiple factors may contribute to the increased rate of adverse drug reactions in the elderly and include an increased number of drugs per patient, some of which may be unnecessary; an increased intrinsic sensitivity to the drugs due to altered pharmacokinetics and pharmacodynamics; the frequent presence of multiple chronic illnesses that may adversely interact with the drugs, and poor compliance.[128,129]

TABLE 4.—*Prescribing Recommendations for the Elderly**

Identify medical illnesses that will affect drug disposition and adjust dose accordingly
Start with low drug doses and gradually increase
Monitor serum concentrations when available
Explain to patient and family the reason for a medication
Expected benefits
Possible side effects
Possible interactions with drugs or foods
Provide a patient with a written list of all medication
Identify each drug by name, list its purpose and describe its appearance
Develop a dosage schedule to match a patient's activity schedule
May use drug calendars to reinforce instructions
Be sure a patient can read instructions and can open container
Use large labeling and easy-open containers when necessary
Be sure patient has access to a pharmacy and can afford prescription
Monitor compliance
Use relatives and other health professionals in home
Request patients bring all drugs to office visits
Maintain complete chart roster of prescription and nonprescription drugs
Periodic review of need for continued drug therapy
Reduce medication to the minimum necessary

*Adapted from Lamy[128] and Royal College of Physicians.[129]

Elderly persons may also fail to use prescribed medication effectively: 25% to 50% of elderly outpatients may not comply properly with their drug therapy, failing to take prescribed medication, taking drugs that were not prescribed or taking medication at incorrect time intervals.[133,134] Causes of poor drug compliance in the elderly include large numbers of drugs; misunderstanding of verbal instructions, often due to cognitive or hearing deficits; poor vision and inability to read prescription labels; an inability to open child-proof containers (found in 25% to 50% of elderly patients), and an inability to afford medication or lack of adequate transportation to reach a pharmacy.[128,133,135]

A number of studies have identified a subset of elderly patients who may be at greater risk for adverse drug reactions or poor compliance or both.[128] These high-risk groups include the "old-old" elderly (aged 75 years or older), women, those elderly living alone, elderly persons who take more than three drugs per day, elderly persons with multiple chronic illnesses, elderly persons with impaired vision or hearing and those with severe physical or mental disability. Although there has been little validation in controlled studies, a number of preventive measures have been suggested to decrease the frequency of adverse drug reactions and to improve patient compliance in the elderly (Table 4).

Urinary Incontinence

The prevalence of significant urinary incontinence increases with age and is estimated at 5% to 20% in community-dwelling elderly persons and 40% to 50% in the elderly in institutions.[5(pp107-135),136] Many of these patients are otherwise ambulatory and have good mental function.[5(pp107-135)] The medical, psychological and social consequences of urinary

incontinence may be disabling to an elderly person. Urinary incontinence may result in skin breakdown, decubitus ulcers, sepsis and even death. It is a source of great personal humiliation and may result in social withdrawal and confinement to the home and may aggravate existing depression. Urinary incontinence may place stress on family and friends. It is a known risk factor predisposing elderly persons in the community to dependency and confinement to an institution. However, with early diagnosis and treatment (pharmacologic, behavioral), most elderly persons with urinary incontinence can be cured or their condition significantly improved, especially the ambulatory elderly.[136]

Despite its high prevalence, tremendous morbidity and relatively good response to treatment programs, urinary incontinence in community-dwelling elderly is frequently not diagnosed. Of the elderly in the community who have incontinence, 20% to 50% are unknown to the health care system.[111,137] This may relate both to the reticence of elderly persons to admit to and discuss urinary incontinence and to the failure of physicians to pursue diagnostic questioning with enough vigor.[138]

Podiatric Care

Common foot problems of the elderly include nail abnormalities, cornifying processes of the foot (calluses, bunions and the like), biomechanical problems—such as arch problems and flat feet—and ulcerations.[139] One study of elderly persons in the community noted a 43% prevalence of foot disorders of mild to moderate severity, some of which had the potential to limit the mobility and independence of the elderly person; two thirds of these disorders were unknown to the patients' primary care physicians.[111] There are no formal studies that confirm the preventive value of podiatric care for the maintenance and improvement of ambulation in the elderly. However, the clinical impression of some geriatricians is that podiatric care may indeed provide such preventive benefits.[5(pp289-302)] It may be beneficial to regularly screen elderly persons for the presence of foot discomfort and examine their feet carefully for the lesions listed above, with referral to a podiatrist as needed. Preventive foot care and education is especially important for elderly persons with occlusive peripheral arterial disease or diabetes mellitus.

Hypothyroidism

Hypothyroidism is a relatively common disorder in the elderly, especially in women. The reported prevalence from community studies varies from 0.5% to 3.8%, depending on the definition of hypothyroidism.[140] The prevalence of overt, symptomatic hypothyroidism in the community is 1.4% in elderly women but less than 1% in elderly men.[141] Subclinical hypothroidism is characterized by an increase in serum thyrotropin (thyroid-stimulating hormone [TSH]) levels with normal or low-normal levels of serum thyroxine (T_4) in the setting of few or absent clinical signs or symptoms.[140] Mild hypothyroidism manifests with minor nonspecific symptoms, elevated TSH and low or low-normal serum T_4 levels.[140] The prevalence of subclinical and mild hypothyroidism in persons older than 60 years may be as high as 7.1% in women and 2.3% in men,[141,142] though other studies have noted lower prevalences.[143,144]

Because of the considerable prevalence of hypothyroidism in the elderly, the Canadian Task Force on the Periodic Health Examination recommended that persons aged 65 and older be screened every two years for hypothyroidism using clinical examination.[12] Others have suggested the routine screening measurement of serum TSH and T_4 levels in view of the difficulties in clinically diagnosing subclinical and mild hypothyroidism in the elderly.[140,142] The critical question is whether thyroid hormone replacement is clinically beneficial to a patient with mild, or especially subclinical, hypothyroidism. If few or no benefits are to be derived from therapy, there is little indication to pursue a vigorous screening program. Recent evidence suggests that thyroxine therapy may be of value to many of these patients, correcting abnormal myocardial function that may be present in up to 50% of patients with subclinical hypothyroidism and relieving subtle hypothyroid symptoms that may be elicited only with intensive questioning.[145,146] Additionally, many patients with subclinical and mild hypothyroidism will progress to overt hypothyroidism, which will be poorly tolerated by some.[140,147-149] Thyroxine replacement therapy in these patients may prevent the development of overt hypothyroidism.[149] However, further studies of the prevalence of hypothyroidism and of the benefit-toxicity ratio of thyroxine treatment of elderly patients with subclinical and mild hypothyroidism are needed before a definite statement can be made about the utility of regular screening.

Comprehensive Assessment and Tertiary Prevention

A comprehensive assessment of an elderly patient includes not only identifying and treating specific medical conditions but also quantifying a patient's physical, mental and social function. The discovery of functional impairment or disabilities guides subsequent rehabilitation efforts. If function cannot be adequately restored, the physician may enlist family or community resources (or both) to help prevent or forestall increasing dependency and possible placement in an institution.[150,151]

The Canadian Task Force on the Periodic Health Examination recommends that primary care physicians comprehensively assess their elderly patients every other year from age 65 to 74 and annually thereafter.[12] However, a comprehensive assessment of disease and function in elderly patients may be complex and time-consuming and require the multidisciplinary skills of allied health personnel; it will therefore be expensive in terms of finances and resources. Is there evidence that such an assessment will improve patient outcome for the elderly?

There is only one controlled trial of comprehensive assessment of elderly outpatients. Tulloch and Moore randomly selected 295 general practice patients aged 70 years and older for a control group that received conventional patient-initiated care and an experimental group that underwent comprehensive assessment of disease and function; these patients were observed for two years.[15] In the experimental group they discovered a large number of previously undiagnosed but treatable medical conditions and many social problems. However, at the end of the two-year study period there was no difference between the groups with respect to medical conditions or functional status. The experimental group did consume more social and health services.

A number of studies have examined the effectiveness of

comprehensive assessment of the elderly in an inpatient setting of geriatric assessment or evaluation units. These elderly inpatients constitute a select group and the results of these studies may not be generalizable to the elderly population at large. These studies have been recently reviewed.[151-153] Most of the studies are descriptive and did not use an experimental design with a control group. Most of these uncontrolled data do suggest that comprehensively assessing elderly inpatients improves patient outcome with respect to diagnosis and treatment of previously unrecognized medical conditions, more appropriate and decreased use of medication, improved physical and mental function, improved emotional state and sense of well-being and lower rates of nursing home placement after hospital discharge.[151,152] Two controlled studies of geriatric assessment units are available,[154,155] along with preliminary results from a third study.[151] One of the studies noted some improvement in function with comprehensive assessment but no change in mortality or in rates of nursing home placement.[154] The other two studies found an improved functional state and lower rates of institutional placement following comprehensive assessment[151,155]; preliminary results from one of these studies also suggest decreased one-year mortality, lower rates of readmission to hospital, and reduced costs in the experimental group.[151]

The disparate results of these studies may relate to patient selection, in that perhaps only certain subgroups of the elderly benefit from comprehensive assessment.[151] Most elderly persons who are relatively healthy and the subgroup with the most severe functional compromise perhaps derive less benefit than those elderly patients who fall in between these two groups.[151,153]

More research is urgently needed to determine the effectiveness of comprehensive assessment of both elderly outpatients and inpatients. Validated preevaluation selection criteria are needed to target those subgroups of elderly patients most likely to benefit from comprehensive assessment.

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Physicians' Own Health—Some Advice for the Advisors

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Information about physicians' health and health practices is sparse and scattered. With a few exceptions, however—notably suicide and substance abuse—it appears that physicians' health and health-promotion activities are at least similar to those of the general public. In some areas, such as smoking cessation, physicians have far outstripped the general public. As physicians gain more insight into their own health and health habits, advice to patients can be realistic and effective. Indeed, several personal health activities, including immunization, have direct, salutary impacts on patient care. Physicians should analyze and change their own health practices as indicated and pay special attention to "high yield" health habits, such as seat-belt use.

(Clever LH, Arsham GM: Physicians' own health—Some advice for the advisors, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:846-854)

This special issue of the journal focuses on how physicians can help their patients promote health and prevent disease, but what about physicians' own health? Although not commonly recognized or discussed, physicians are people. They are people with unusual responsibilities and challenges, but basically people still. Do physicians have unique health problems? What information is available about physicians' health maintenance practices? Do some of these practices also affect patient care? What advice is available to improve physicians' health?

In this article we briefly review current literature, comment on health maintenance opportunities for physicians and, finally, offer the challenge of health-to-health combat with the Harvard Medical School Faculty.

Physician Life Expectancy and Mortality

Most information about physicians' lives and deaths is gathered by the American Medical Association (AMA) and includes reports, clippings and correspondence, often backed by death certificates. The most comprehensive study using this information calculated age-adjusted death rates and standardized mortality ratios (SMRs).[1] (An SMR is the actual versus expected number of deaths in relationship to a defined standard; an SMR of less than 100 suggests that the study population has a lower mortality than the comparison group, the United States white population.) This study showed that physicians have a two- to three-year longer life expectancy than their same-aged US counterparts and that life expectancy has improved substantially—at least for male physicians—since 1925 (and has improved more than that of white American men). Female physicians were shown to have a lower age-specific mortality than male physicians but a higher SMR. Thus, women physicians are "healthier" than male physicians, but less healthy than the US female population. Male physicians on the Pacific Coast and in New England had an 8% lower mortality than expected. SMRs of male physicians were found to vary by specialty: greater than 100 for those in general practice and pulmonary medicine, 96 for psychiatrists, 87 to 89 for internists and general surgeons, 72.5 for pediatricians and 64.8 for the lumped "other" specialties—primarily public-health oriented physicians and some subspecialists.[1] In contrast, a cohort study of more than 1,000 Harvard Medical School graduates found no differences in longevity among specialty groups.[2] Thus, life-span statistics are generally encouraging despite 1960 census data showing that physicians worked 55.5 hours per week, and 48.2 weeks per year compared with 40.4 hours per week and 44.5 weeks per year for all professionals.[2] Table 1 shows that except for arteriosclerotic vascular disease and for suicide, the causes of death for physicians do not differ greatly from those of the general population.

Interestingly, not only do physicians work more *hours* than others but they also work more *years* and therefore have a shorter retirement—3.1 years for physicians versus 7.8 years for the general population.[4] A recent Canadian study confirmed these population statistics: 93% of 58 surveyed physi-

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ABBREVIATIONS USED IN TEXT
AMA = American Medical Association
JAMA = *The Journal of the American Medical Association*
SMR = standardized mortality ratio

TABLE 1.—*Causes of Death in Physicians and the United States Population**

	Physicians in 5 States Percent	*US Population Percent*
ASCVD†	48.4	58.2
Cancer	21.6	20.9
Chronic lung disease	3.4	2.8
Suicide	2.4	1.3

*A study of 1,258 physician deaths in Arizona, California, Michigan, Oregon and Pennsylvania. Report of the AMA Council on Scientific Affairs, Report G(1-82), presented by William D. Dolan, MD, chair. From Dychtwald.[3]

†Heart disease, cerebrovascular disease and arteriosclerosis.

cians whose average age was 71 years were still in practice—72% involved in direct patient care—and 65% had no retirement plans.[5]

Suicide

The study of suicide in physicians has been marked by methodologic problems. It has long been suspected that suicides are underreported in AMA records and the AMA journal (*JAMA*). Indeed, Rose and Rosow showed that *JAMA* reports of California physician suicides listed only half of death certificate-proved suicides as "definite"; other causes were suspected, undisclosed, incorrect or omitted.[6] Valid conclusions are impeded by lack of age, sex and professional groups for comparison and, above all, inadequate numbers.[7-10] The following provisional conclusions can be drawn, however.

- Male physicians probably have twice the annual suicide rate of the white male population.[6]
- Female physicians probably have slightly more than triple the annual suicide rate of the US white female population.[8,9]
- No real inference can be drawn from suicide rates by specialty because of small numbers.
- Other professionals, including dentists, pharmacists and chemists, probably have substantially higher annual suicide rates than physicians.[6,7]

A recent British study based on government statistics showed the SMR for suicide in physicians younger than 65 to be more than three times that of the general English and Welsh male population but 1/5 that of pharmacists. Unmarried female physicians had an SMR 2½ times greater than the general unmarried female population but 1/5 that of female pharmacists.[11] These dramatic statistics warrant further investigation. Steindler proposed that many precursors of suicide in physicians parallel those of the general population: "depression, prior suicide attempt, alcohol and drug abuse, financial troubles, death of a close relative in childhood, death of a relative, and impaired physician health."[12] He also suggested that "professional isolation by specialty or geography, marital discord, unrealistic expectations of one's self and one's ability to cure disease, and the emotional battering of being confronted with [the] daily prospect and often actuality of pain and death" were additional problems faced by physicians.

Personal Health Practices

In three recent publications the broad spectrum of physicians' personal health practices was surveyed.[13-15] Indeed, readers of the *WJM* can compare their habits with those of the Harvard Medical School faculty by taking the self-test at the end of this article (see Figure 1). Good health habits practiced by physicians include dietary moderation, seat-belt use, temperate drinking habits and avoidance of tobacco smoking. According to one 1977 study, 21% of physicians in the United States smoked cigarettes; 14% of physicians in Massachusetts smoked in 1978. This compares favorably with the 39% of men in the US who smoked during that time.[14] A Massachusetts study of physicians and attorneys showed that 50% of physicians versus 40% of attorneys practiced dietary restrictions, such as reduced fat, salt and calories. Also, more physicians than attorneys used seat belts; 3% of physicians and 9% of attorneys reported drinking problems; gardening, not often an aerobic effort, was reported as the commonest recreational physical activity by both groups.

As seen above, the few studies of across-the-board physician health maintenance practices have included information about seat belt use. These data are pertinent because (1) the US Department of Transportation's National Highway Safety Administration estimates that the average American has a one in three chance of suffering a disabling injury from an automobile collision during his or her lifetime, and (2) it is estimated that the risk of serious injury or death can be reduced by more than half by simply wearing seat belts every time a person drives or rides in a car. Regular use of safety belts would reduce yearly traffic deaths by at least a third to a half.[16] Fortunately, seat-belt use by drivers in West Coast cities increased from 14% in 1981-1982 to 20% in 1983. This improvement is more than twice the 2.6% average change in cities nationwide (Calvin Burkhart, Regional Administrator, Region IX, National Highway Traffic Safety Administration, written communication, May 1984). Physicians in the West may parallel the 73% of Massachusetts physicians who buckle up.[13] Surely, physician use of seat belts is consistent with findings that directly correlate educational level and other "good" personal health practices—such as, nonsmoking and regular visits to a dentist—with seat-belt use.[17]

Smoking Habits

Physicians have given up smoking at a rate higher than any other professional group.[18,19] The proportion of internists smoking cigarettes decreased from 60% in 1945 to 22% in 1967 and 17% in 1975.[20] Sachs surveyed 594 of 2,207 American pulmonary disease specialists at the 1983 American Thoracic Society Annual Meeting; 4.6% said they smoked cigarettes and 7.4% a pipe or cigars.[21] Among California physicians, the percentage of cigarette smokers has declined from about 53% in 1950 to about 10% in 1980.[22] For other American men, the percentage of smokers has declined only from 53% to 39%. Enstrom chose to use this "natural experiment" to study mortality trends among California physicians who stopped smoking compared with the general public. He studied the mortality of a cohort of more than 10,000 California male physicians from 1950 through 1979 and found

that the SMR for lung cancer among California male physicians, compared with American white men, declined from 62 in 1950-1959 to 30 in 1970-1979. There were similar declines for other diseases related to smoking, such as ischemic heart disease (106 to 71); bronchitis, emphysema and asthma (62 to 35) and for other smoking-related cancers of the esophagus, buccal cavity and respiratory system (100 to 63). For causes of death not strongly related to smoking, the SMR remained relatively constant. These data are generally consistent with a similar study of British physicians.[23,24] Interestingly, Enstrom also compared mortality patterns among all physicians with a subgroup of 1,180 Loma Linda University medical graduates, assumed to be nonsmoking Seventh Day Adventists. The overall SMR declined from 84 in 1950-1959 to 67 during 1970-1979 for all physicians, but only from 62 to 56 for Loma Linda graduates. This suggests that the decrease in mortality from lung cancer and ischemic heart disease among California physicians was largely due to smoking cessation. While other factors may account for the decline in mortality from ischemic heart disease (such as improvement in other health habits), they are not likely to have had a substantial impact on mortality from lung cancer.

Personal Health Maintenance and Patient Care

Immunization

A number of physicians' personal health habits (good and bad) have direct impact on patient care. These include heavy drinking and abuse of other substances, stress and fatigue management and one rarely considered practice, immunization. To decrease the risk of teratogenesis and absenteeism, a number of agencies and institutions have recommended rubella screening and immunization of hospital personnel.[25] Reports have shown that only 20% of susceptible physicians have been immunized, compared with 53% to 66.2% of all employees.[26,27] The lowest vaccination rate (1 out of 11 susceptible) in the Los Angeles County/University of Southern California Medical Center report was among obstetricians and gynecologists; 31% of susceptible pediatricians allowed vaccination.[27] Experience with hepatitis B vaccine in hospitals has paralleled that of rubella.[28] Although 16% of physicians have serologic evidence of hepatitis B infection (thus showing that physicians *can* contract this potentially disabling, fatal disease), very few exposed physicians (house staff or attending) have been vaccinated. This not only leaves physicians susceptible to the disease, but also raises the possibility of physician-to-patient disease transmission.

Substance Abuse—Alcohol and Drugs

Because of concerns about patient care and personal and family tragedy, increasing attention has been paid to the problem of impaired physicians. Alcohol abuse and other drug dependence have been spotlighted as important elements. In the past, physicians were generally believed to be more susceptible to alcohol and drug abuse than the general population. Although large-scale reliable studies of these problems are not available, more and more studies of impaired physicians are being done.[29-32] In a recent study at the Mayo Clinic, 453 physicians attending a continuing education course were asked to fill out a self-administered alcoholism screening test; there was an 88% return rate.[33] The prevalence of serious alcohol dependence and actual alcoholism was 7% among physicians who did drink. This percentage is virtually the same as for a similarly surveyed general outpatient population.[34]

Drug abuse is still considered to be somewhat more prevalent among physicians than the general public.[29] A 20-year longitudinal follow-up study of 45 physicians and 90 controls showed that the use of tranquilizers, sedatives and stimulants was greater among physicians than among controls.[35] The regular use of sedatives was almost three times as great as for controls, and the regular use of tranquilizers was about twice as frequent, but not statistically significant. (The study showed no difference for alcohol use.) Data from the California Board of Medical Quality Assurance Treatment and Rehabilitation Program showed that large numbers of impaired physicians abuse drugs. Of 80 physicians in treatment programs, 31 were being treated for drug abuse, 18 for alcohol abuse, 13 for both alcohol and drug abuse and the remaining 18 for various combinations of mental or physical illness and substance abuse.[30] Encouragingly, an albeit incompletely controlled Mayo Clinic study found that the prognosis for favorable outcome was greater for physicians than for general patients, and that the prognosis was not related to the severity of the problem. Furthermore, and somewhat unexpectedly, they found that the physicians with drug addiction seemed to do better than those with alcoholism.[29]

Special Pressures and Responsibilities

If anything sets physicians apart from others, it is the special pressures and responsibilities that are intrinsic to the medical profession. Healthy responses to these demands may well determine a physician's ability to assure high-quality patient (and personal) care. McCue outlined several difficult areas.[36] Some, such as the need to deal with suffering (and sometimes inflict suffering), the need to allay patients' fears, the privilege of dealing with private aspects of a patient's body and life and the frequent presence of death, relate to emotional aspects for which our society has developed strong cultural codes and behavior. Other intrinsic demands derive from encountering situations for which physicians have not always been well prepared—such as "problem" patients—or with demands that are unrealistic—such as requests for certainty when only uncertainty is possible. Hilfiker explored the relative expectations of perfection that society (and physicians) have of physicians: no mistake allowed.[37] An illogical attitude of immunity to problems and diseases that may afflict others—what might be called the "physician invulnerability syndrome"—may prevent healthy coping. Some mental mechanisms—and a healthy sense of humor—help contend with problems medicine presents, but excessive denial is not beneficial.

A longitudinal study of Case Western Reserve School of Medicine graduates found that the major dissatisfactions among physicians still related to time pressures but that several new sources of stress are being described—malpractice suits, having to give up certain aspects of medical work, the threat of physical harm and certain features of peer review.[38] Other new pressures include decreased autonomy, increased control (from new regulations), increased competition due to more doctors being trained, the emergence of greater roles for

other health professionals and decreased financial rewards.[39] On the other hand, medicine has many intrinsic rewards, pleasures and privileges that may help account for physicians' perhaps surprisingly good health.

Comments and Recommendations

Although information about health promotion for physicians and the general public is incomplete and inconclusive, some comments and recommendations are in order. Despite the special responsibilities that the practice of medicine creates, physicians still make conscious decisions about their lives based on their own personalities and assessment of benefits and costs, just as everyone does. The steps suggested for physicians will therefore be very similar to those that physicians can recommend to their patients.

- Assess where you are. What is the current state of your health? What are the factors in your life that contribute to your health or enhance the likelihood of disease?
- Consider your options based on your current health practices and your own values, personality and life. Here is where your own formula comes into play. Only you can find the balance between the pleasure you gain and the risk you incur—for instance, the principle of rotating dietary "toxins" will allow occasional indulgence.
- Once decisions are made, provide incentives and remove barriers to change habits. These are powerful tools. Just as you would with your patients, ask yourself what barriers exist in improving your health and think of ways that barriers could be reduced or eliminated. Ask yourself what things give you pleasure. Find ways to make those rewards contingent on the changes you are trying to accomplish—for example, turn on the radio *after* you have fastened your seat belt.
- Find ways to document the changes—jot progress on a graph and post it on a mirror. Overall, follow Watts's call to put personal health maintenance high on your professional agenda in order to help your patients[40] *and* put it high on your personal agenda in order to help yourself.

The following suggestions merit your consideration, at least:

- Get help when you need it. The "physician invulnerability syndrome" is a serious risk factor.
- Wear seat belts *every* time you drive or are a passenger. This is an easy, "low-cost" item.
- Stop smoking. In addition to the long-term gains resulting from smoking cessation, there are some short-term gains that may be important, such as less coughing and more breath.
- Get immunized against the hepatitis B virus if you come into contact with blood or blood-contaminated patient products. This is another easy, low-cost item, as are tetanus and rubella shots.
- Drink alcohol in moderation, if at all. The possible positive effects of small amounts[41-44] must be weighed against considerable negative consequences of excessive alcohol.[45] Also, avoid recreational drugs.
- Consider a form of aerobic exercise that you *enjoy*. If you do not enjoy it, it will be difficult to continue.
- Consider decreasing the cholesterol and saturated fats in your diet and increasing the vegetables, fruit and whole grains. Pasta is fine, garlic is great and olive oil is neutral.
- Consider developing interests outside of medicine that give you satisfaction. These can range from traditional hobbies to involvement in public life, which can contribute to the public health and certainly help manage professional pressures. Benjamin Rush may have set the tone for public service by American physicians. He was a signer of the Declaration of Independence, Surgeon General, Treasurer of the Mint and advocate for the rights and humane care of the mentally ill. Now as then, physicians can volunteer in underserved areas in the United States and abroad or as citizen members of governing boards of service, cultural and educational organizations. They understand the health implications of war and can inform the public; they can participate in debate about health care delivery and financing; they can encourage and be involved in planning for natural disasters. David Bates suggests two caveats for physicians-as-citizens: "The necessity of integrity and the avoidance of political polemic."[46]
- Finally, a word about retirement. Regardless of previously mentioned findings, some physicians do retire. Although this transition is a time of vulnerability, planning can be an enormous help. New activities can be a source of continued success and help maintain self-esteem. Important factors include fitness, freedom, finances, family, fun and flexibility. One helpful planning resource is a 129-item bibliography on physician retirement developed by the AMA Division of Library and Archival Services in 1980.

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See addendum next page.

Addendum

Figure 1.—Personal health practices—How do you compare to the Harvard Medical School faculty? (Excerpted from the June 1982 issue of *The Harvard Medical School Health Letter* © 1982 President and Fellows of Harvard College.[13])

PERSONAL HEALTH PRACTICES
HOW DO YOU COMPARE TO THE HARVARD MEDICAL SCHOOL FACULTY?

The following survey of personal health practices was just completed by 595 members of the Harvard Medical School faculty. Check the answers as they apply to you; then go on to see how you compare with those who preach as well as practice.

1. Do you smoke cigarettes? Yes ☐ No ☐
   If so, how many a day?____ If not, are you a former cigarette smoker? Yes ☐ No ☐
2. Do you use tobacco in any other form on a daily basis? Yes ☐ No ☐
   If yes, what form? Pipe cigar snuff chewing tobacco
3. Do you use a sleeping pill more than three times a week? Yes ☐ No ☐
4. Have you had a routine health exam during the past two years? Yes ☐ No ☐
5. Do you use seat belts routinely? Yes ☐ No ☐
6. Do you use aspirin on a daily basis to protect against vascular disease? Yes ☐ No ☐
7. Do you usually take an antibiotic if you develop an upper respiratory infection? Yes ☐ No ☐
8. Do you jog or do equivalent aerobic exercise for 20 minutes (or more) at least three times a week? Yes ☐ No ☐
9. If practicing contraception, do you (or your partner) use contraceptive pills? Yes ☐ No ☐
10. If female, do you routinely perform self-examination of your breasts? Yes ☐ No ☐
    If male, do you routinely perform self-examination of your testes? Yes ☐ No ☐
11. Do you eat breakfast? Yes ☐ No ☐
12. Do you weigh more than 10 pounds above what you'd like to weigh? Yes ☐ No ☐
13. Do you take more than 2 alcoholic drinks a day? Yes ☐ No ☐
14. Do you restrict your consumption of red meat to 3 times a week or less? Yes ☐ No ☐
15. Do you try to maintain a high bran or fiber content in your diet? Yes ☐ No ☐
16. Do you drink coffee? If yes, how much?____ Yes ☐ No ☐
17. Do you restrict your egg intake to 3 per week or fewer? Yes ☐ No ☐
18. Does your household use margarine (as opposed to butter)? Yes ☐ No ☐
19. Do you visit your dentist for a check-up at regular intervals? Yes ☐ No ☐
20. Do you floss your teeth daily? Yes ☐ No ☐
21. Do you take vacations during which no work is done? Yes ☐ No ☐
22. Do you take a daily multivitamin? Yes ☐ No ☐
23. Do you ever make purchases in stores devoted exclusively to health foods? Yes ☐ No ☐
24. Do you use vitamin C to protect against colds? Yes ☐ No ☐
25. Do you take a laxative or enema if you do not have a bowel movement for 2 days? Yes ☐ No ☐

THE ANSWERS OF OUR FACULTY

Now that you've gone on record, here's how our faculty responded... along with a bit of commentary on each set of answers. (A description of how the survey was done and some further words on it appear in this month's Medical Forum.)

1. Do you smoke cigarettes? Yes 8% No 92%
   If not, are you a former cigarette smoker? Yes 38% No 62%

There's no question that doctors have not only read the warnings but have also seen the consequences "close up" among their patients with heart disease, cancer, and emphysema. Eight per cent still smoke cigarettes as compared with 32% of the general population. And only 13 of 49 reported smokers exceeded one pack a day. The number of *former* cigarette smokers — 34% of all responders — is also impressive.

2. Do you use tobacco in any other form on a daily basis? Yes 11% No 89%

Pipes had it over cigars by 3 to 1. No one chewed tobacco and 2 used snuff. So long as inhaling is avoided, the danger of lung damage is considerably reduced.

3. Do you use a sleeping pill more than three times a week? Yes 2% No 98%

While the low use of sleeping pills might suggest a high level of serenity, we've been at too many faculty meetings to believe that. More likely, it's a healthy desire to avoid drugs that can be habit-forming. The frequent use of some sleeping pills can even interfere with normal sleep patterns.

4. Have you had a routine health examination during the past two years? Yes 54% No 46%

We were surprised to find that so many have, given the common notion that doctors are the last ones to seek a routine check-up. As might be guessed, older individuals did so more frequently. Regular health exams were obtained by 41% of our faculty in their 30s, 54% in their 40s, 65% in their 50s, and 80% of those over 60.

5. Do you use seat belts routinely? Yes 73% No 27%

Hooray! While hardly perfect, the high rate of seat belt use is testimony that at least some common sense prevails in ivory towers. And our guess is that doctors who work in emergency rooms that receive auto accident victims approach 100% in *their* seat belt use.

6. Do you take aspirin on a daily basis to protect against vascular disease? Yes 7% No 93%

It has been proposed that aspirin taken in low dosage will prevent heart disease and strokes by inhibiting blood clotting. However, few of our faculty seem to act on what remains an unproven hypothesis.

7. Do you usually take an antibiotic when you develop an upper respiratory infection? Yes 3% No 97%

So much for how we treat our own common colds. We hope that our readers will feel secure without antibiotics for theirs. (Chicken soup has a lower incidence of side effects.)

8. Do you jog or do equivalent aerobic exercise for 20 minutes (or more) at least three times a week? Yes 49% No 51%

Vigorous exercise is popular among faculty of all ages and both sexes. While "feeling good" and "looking good" are important reasons for exercise, the kind of exercise we asked about is also believed to promote cardiac fitness.

9. If practicing contraception, do you (or your partner) use contraceptive pills? Yes 5% No 95%

Of the two-thirds of our responders who practice contraception, the use of the pill by the female partner is strikingly low. One reason, given that 99% are beyond age 30, is that they have probably completed their families, making tubal ligations and vasectomies more acceptable. Also, vascular complications from the pill are higher in older females, an additional reason for seeking other measures.

10. If female, do you routinely perform self-examination of your breasts? Yes 72% No 28%
If male, do you routinely perform self-examination of your testes? Yes 36% No 64%

Early detection of these cancers leads to earlier treatment and a greater number of cures. Self-examination is easy. We'd like to see both men and women achieve 100% on this one.

11. Do you eat breakfast? Yes 78% No 22%

A point of interest for some, perhaps. It may not be crucial to start the day off with a good meal, but it may indicate a greater awareness of the importance of nutrition.

12. Do you weigh more than 10 pounds above what you'd like to weigh? Yes 29% No 71%

While 29% of our faculty are not as trim as they'd like to be, in most cases it's apt to be more a concern for appearance than for health. A few extra pounds are usually not a health hazard.

13. Do you take more than 2 alcoholic drinks a day? Yes 7% No 93%

Two ounces of alcohol a day may actually be beneficial, but more that this should be cause for concern.

14. Do you restrict your consumption of red meat to 3 times a week or less? Yes 44% No 56%

A surprising number of faculty restrict red meat consumption, probably because of evidence linking red meat consumption to bowel cancer, and possibly to avoid the animal (saturated) fat present in red meat.

15. Do you try to maintain a high bran or fiber content in your diet? Yes 41% No 59%

High fiber diets clearly help constipation. Some believe such diets also decrease the risk for bowel cancer by promoting more rapid evacuation of carcinogens from the colon.

16. Do you drink coffee? Yes 83% No 17%

Of those who drink coffee, 47% have 2 cups or fewer a day, 45% average 3 to 5 cups, and only 8% exceed 5 cups. Many of the health problems purported to be linked to coffee remain in question on careful study—but all would agree that too much coffee can cause jitteriness, palpitations, and insomnia.

17. Do you restrict your egg intake to 3 per week or fewer? Yes 79% No 21%

A surprisingly high degree of egg restriction, we thought, presumably due to concerns about cholesterol.

18. Does your household use margarine (as opposed to butter)? Yes 69% No 31%

Again, it's probably concern for cholesterol levels that prompts the use of margarine, which is high in polyunsaturated fat as compared to butter. Margarine is also less expensive.

19. Do you visit your dentist at regular intervals? Yes 84% No 16%

Good sense. Fewer root canal jobs, we hope.

20. Do you floss your teeth daily? Yes 41% No 59%

The greatest cause of tooth loss among adults is periodontal disease, not caries. And flossing should help remove the plaques that contribute to periodontal disease.

21. Do you take vacations during which no work is done? Yes 83% No 17%

Probably a healthy practice, but hardly an essential one. Several responders described their golf games as more work than play.

22. Do you take a daily multivitamin? Yes 14% No 86%

There's no real need for vitamin supplementation if one's diet is normal and special circumstances (e.g., pregnancy, digestive disorders) are not present.

23. Do you ever make purchases at stores devoted exclusively to health foods? Yes 25% No 75%

Many "health foods" are overpriced in respect to their true nutritional value. At times, they may produce a positive placebo effect of "feeling good."

24. Do you use vitamin C to protect against colds? Yes 14% No 86%

Few seem to believe that vitamin C really works. Or else they find that daily pill taking is more bothersome than a few days of sneezing and dripping.

25. Do you take a laxative or enema if you don't have a bowel movement for 2 days? Yes 3% No 97%

There's wide variation in bowel habits among normal people, and apparently few of our faculty believe the ads promoting medications to achieve "regularity."

Physicians as Patient Teachers

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Physicians have a central role in educating patients and the public in the elements of personal health maintenance. To be an effective teacher, one must recognize the learning needs of each patient and use methods of information transfer that will result in comprehension and compliance. To bring about a change in life-style, one must also have an understanding of a patient's health beliefs and the determinants of human behavior. Using this information together with behavior modification strategies, physicians can forge an effective partnership with patients working toward the goal of optimum health.

(Brunton SA: Physicians as patient teachers, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:855-860)

> *The physician's function is fast becoming social and preventive, rather than individual or curative. Upon [physicians] society relies to ascertain and through measures* essentially educational *to enforce, the conditions that prevent disease and work positively for physical and moral well-being.*
>
> ABRAHAM FLEXNER, 1910
> *(emphasis added)*

The role of doctor as educator is implicit from the etymology of the word "doctor," which is from the Latin *docere,* "to teach." However, despite the educational reformist Flexner's perception, it is only within the past decade that any emphasis has been placed on patient education skills either in medical school or in postgraduate training programs.

At the same time, the public appears increasingly interested in learning about medicine and health, and in making inroads into areas that previously were the sole domain of health care providers. Attesting to this are the burgeoning sections in bookstores dealing with health-related matters and the popularity of such reference books as the *Physicians' Desk Reference.*[1] The mass media's focus on health has resulted in medical updates being shown on most news shows, and this has now culminated in a cable television network whose task it is to provide 24-hour programming of predominantly health-related topics. This particular network also screens continuing medical education programs for physicians that have gained wide public viewing despite the highly technical language and the specialized nature of the material.

What Is Patient Education?

This widespread dissemination of information about medicine and health has resulted in the public having a general understanding about what constitutes an unhealthy life-style. That is, smoking, drinking to excess and overeating are now widely regarded as unhealthy behaviors.

Patient education, however, implies more than just imparting facts. A useful operational definition was developed by a National Task Force on Training Family Physicians in Patient Education:

> Patient education is the process of influencing patient behavior, producing changes in knowledge, attitudes, and skills required to maintain or improve health. The process may begin with the imparting of factual information, but it also includes interpretation and integration of the information in such a manner as to bring about attitudinal or behavioral changes which benefit the person's health status. Thus, patient education not only involves the world of medical scientific facts, but in its process, is also closely interwoven with psychology, sociology, behavioral science, and cultural anthropology.[2]

Patient education and preventive health services constitute a major portion of the care provided by physicians. An extensive statewide study in Virginia found that the most frequent diagnosis made by family physicians was "other medical exam for preventive and presymptomatic purposes," accounting for 8.3% of patient visits,[3] and it has been estimated that between 19% and 35% of the time primary care physicians spend in direct patient care involves health education and counseling.[4]

Physicians are extremely important agents of change who have significant influence over their patients, a relationship that can be central to patients' ability to attain and maintain health. To practice effective patient education, one must understand the person and have a grasp of some fundamental concepts that can facilitate an effective partnership in health.

An ambiguous message is given by physicians who display inappropriate health behavior.[5] Physicians who attempt to alter their own risks and achieve a greater degree of health will gain insight into the difficulties of behavior change, and

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they will then have an opportunity to share experiences with their patients and thus enhance their credibility.

Pedagogy Versus Androgogy

The predominant educational model is that of a passive dependent learner in a subject-centered curriculum. Grades are based on the mastering of content with an assumption that students will later find application for this knowledge. This has been described as the pedagogic model (from the Greek *paidos* meaning child).

An alternative model, androgogy (from *andros* meaning man) implies a more mature learner who is directed to learn skills for immediate application. The material to be learned is based on a needs assessment and the course material is problem-oriented rather than simply described by subject. Perhaps most important, the relationship between teacher and students is cooperative and born of mutual respect.[7]

The pedagogic model of learning is perhaps the most familiar to us and is therefore the most frequent method used in patient teaching. The rise of the "consumer mentality" and a desire by patients to be more assertive in the therapeutic relationship has discouraged a passive and dependent role. Because most patient education is education of adults, an androgogic model may be a more useful concept for planning patient education activities. This provides patients with an opportunity to define their educational needs and to be inquisitive while exploring new areas of knowledge. It discourages the dependence that can create resistance and resentment.[8]

Doctor-Patient Relationship

The importance of a quality interaction between patient and physician cannot be overemphasized.

A patient's desire for knowledge and a physician's ability to communicate this information are to a large extent responsible for the degree of satisfaction and compliance that can be achieved.[9,10]

Studies of compliance consistently focus on aspects of the doctor-patient relationship that are either conducive to or counterproductive to a patient's adherence to the treatment regimen. Examples of positive factors include a patient's perception of the physician as interested, friendly and empathic.[9-12] Other factors include the amount of time spent with a patient and the degree to which patients' expectations are met.[9,10] Examples of factors that inhibit compliance include poor communication skills exhibited by a physician,[9,13] failure to give feedback[14] and office procedures that result in a delay in being seen.[10,13,15]

The potency of this relationship and its ability to effect life-style change were illustrated in some studies that showed that simply giving advice to a patient to stop smoking was a significant motivator for abstinence.[16] When this advice was provided firmly and emphatically, the chance for abstention was significantly greater.[17]

In a recent study in Massachusetts examining primary care physicians' role in health promotion, most of the respondents were of the opinion that it was definitely physicians' responsibility to educate patients about risk factors. However, while they were prepared to counsel patients regarding unhealthy life-styles, only 3% to 8% of the respondents thought that they were "very successful" in helping patients achieve changes in behavior, although an additional 40% to 57% thought that they were at least "somewhat successful" in one or more areas.[18]

A physician's feeling of inadequacy and defeat when faced with a patient who is on a fast track to life-style-related illnesses is understandable. Nevertheless, the need for appropriate intervention is imperative. Physicians should adopt a teaching and counseling role to increase patients' awareness and skills necessary to effect life-style changes.

Human Behavior

The number of variables that come into play in a patient's decision to undertake a particular health behavior has been the focus of significant study and theory.

The *health belief model* and the *health locus of control theory* incorporate principles of behavior that facilitate understanding of a patient's motivation and the likelihood of their adhering to a particular regimen. These concepts also provide insight into different strategies that may be effective in encouraging individual health promotion.

In the health belief model, several factors are proposed that can predict a patient's likelihood that a particular therapeutic or preventive action will be undertaken. These are the perceived level of personal susceptibility to a particular illness or condition; the perceived degree of severity or seriousness of the illness should it occur; the assessment of the potential benefits for the recommended action in preventing or reducing susceptibility or severity, and the perceived barriers related to the particular actions, which include the estimates of physical, psychological, financial and other costs.[19]

This suggests that a patient's interpretation and perception determine a particular health behavior and that these may be modified by a number of personal and environmental factors. The model also proposes that various stimuli or "cues to action" are necessary to motivate change in health behavior or to make persons consciously aware of their feelings about their condition. These cues can include mass media campaigns, illness in a family or a personal physician's advice.[20]

The *health decision model* represents an evolution of this paradigm. It incorporates the major strengths of the health belief model but additionally addresses patient preferences, including decisions regarding trade-offs between benefits and risks and quality and quantity of life and emphasizes the process by which a patient interprets information.[21] This model emphasizes the significance of patients' feelings about their health and the decisions that are affected by these feelings. The model reinforces the intuitive awareness that by incorporating a patient's preferences into a proposed regimen, the likelihood of success is increased significantly.

Physicians also need to have an understanding of each person's family and social networks because they have an important role in a patient's decision-making process.[22-24]

The locus of control theory reflects persons' perceptions of the source of their power to effect change in particular life events. Within this psychological construct is described a continuum with one end of the scale reflecting those persons who believe in fate, luck, chance or powerful others. This is the external locus of control. On the other end of the spectrum are those who feel totally self-determined and who believe that they have the ability to realize goals once set. These persons are known as "internals."[25]

It would be rare for a person to be either totally internal or

external in all areas of life, but in most instances each person is nearer one end of the continuum than the other.[26] This theory is useful in predicting both health and sick role behaviors, with "internals" taking greater responsibility in undertaking and maintaining positive health behaviors.[27]

This has important implications for the patient education process. "Internals" respond better to programs that provide more information, have opportunities for decision making and responsibility and rely on self-motivation and self-reward. On the other hand, "externals" have more success with group strategies and support; with knowledge, training and experience, however, they can generally develop greater self-reliance.[26]

Working with patients' belief systems and in some instances reeducating them regarding beliefs, myths and misinformation requires a careful assessment of these beliefs and attitudes with open-ended questions and a tolerant attitude.

These theoretic frameworks emphasize the importance of thorough patient interviews about not only life events, but also patients' perceptions of themselves, their conditions and their ability to effect change. By aligning new information with some aspects of patients' previously held beliefs, suggestions can be presented in such a way that they are able to accept aspects of these new attitudes while discarding some of their old beliefs.[28]

Influencing Behavior

By understanding a person's "reasons" for a particular unhealthy activity, one can gain insight into mechanisms that might be used in behavior change. The perception of danger and the arousal of fear regarding a particular action can be important factors in assisting patients to consider undertaking change. Fear per se, however, may not necessarily motivate change, but may provoke alternate mechanisms such as denial.[6,29] To be effective, advice against unhealthy behavior must be accompanied by significant information and support that convinces patients that they are capable of achieving the desired behavioral change. This should be directed to helping them feel some control in a situation despite previous evidence to the contrary.

Physicians should be aware that patients receive a lot of contradictory information. Advertising stresses the sexual rewards of smoking, the comforting effects of empty calories and the social benefits of drinking.[30] These influences can be reinforced by the attitudes of a patient's peer group.

The personal relationship that develops between a patient and that person's physician can provide an unequaled opportunity for intervention that cannot be produced by public education campaigns.[31] This unique relationship can enable physicians to help patients gain insight into the meaning of their behavior and consider alternatives. This can then lead to a significant breakthrough, that of gaining patients' commitment to *attempt* behavioral change.

Using the precepts of the health behavior model, a consultation can emphasize the importance of the risk, the potential for personal susceptibility, the value to the persons in making a change and the ability of persons to achieve change, in such a way as to activate patients to consider reforming their unhealthy life-styles.[32] The decision to actually make a change is based on a psychological readiness and acceptance of the information presented to patients, coupled with a belief in their ability to effect changes.

A valuable mechanism that may be useful for developing patients' insights into the danger associated with their behavior is a risk-appraisal. Use of these programs in conjunction with consultation with a physician can provide graphic evidence of a patient's life-style risks and the benefits of behavioral change. Taking into consideration the factors involved in a patient's decision to undertake a particular preventive activity as elucidated in the health behavior model, the use of this tool can provide an invaluable adjunct of consultation.

Another opportunity to bring about awareness on behalf of a patient is the "teachable moment." This is an opportunity for heightened receptiveness occasioned by an experience in the patient's life that brings about an understanding of the need for life-style changes. This may be initiated by the death of a relative, by the occurrence of new symptoms or merely by an expression of a willingness to learn.[33]

The ability of persons to transform their behavior is influenced by the feeling of control they have over their life as elucidated within the health locus of control theory. This is affected by their previous success or failure at achieving a life-style change. It is important for physicians to be aware that for many patients, success will be preceded by several abortive attempts; in this process, however, patients gain experience in methods of altering behavior. This should serve to remind physicians not to become disheartened by initial failures of patients to effect change, but rather to support them in their further attempts by encouragement and by offering different strategies for success.

It is important that physicians maintain the viewpoint that their role is that of a supportive consultant and that it is the patients' responsibility and in their best interests to develop risk-reducing behavior. Attempts by patients to transfer the locus of control over to a physician should be resisted.

Modifying Behavior

The work of Pavlov, Skinner and others provides further understanding that the determination of any individual behavior can be viewed as a process of antecedents and consequences. The antecedents set the stage for behavior and the consequences determine the frequency and the tendency that the activity will be repeated.[34]

This is the underlying theory behind behavior modification, which is directed at controlling these antecedents (stimuli or cues) and consequences (rewards or punishments). Habits are based on learned patterns that are developed between antecedents, behaviors and consequences. For example, a person using the antecedents of anxiety plus the availability of cigarettes will exhibit the behavior of smoking with the consequence of a short-term reduction in anxiety. Because the effect is desirable, this behavior is reinforced and the presence of stressful situations will continue to serve as a cue for the smoker to use cigarettes. Although long-term harmful consequences exist, it is apparent that short-term and immediate outcomes are more effective in influencing behavior.

Once a pattern has been established, the cue alone may be enough to instigate a particular behavior. For example, if a person uses alcohol to relax on arriving home from a stressful day at work, the mere act of coming home from work may

determine that that person will start drinking whether or not stress was involved on that particular day.[34] This cycle of behavior can provide insight into strategies that might be used in facilitating change by substituting different behaviors and modifying or controlling antecedents and consequences.

The principles of behavior modification offer health care professionals the opportunity to provide patients with an understanding of their behavior, establishing a method of control and consequently instituting new behavioral patterns. A physician's task is to assist patients in developing an appropriate program to achieve these desired actions.

Steps to Behavioral Changes

The first step of this process is to define the problem accurately in behavioral terms. One should attempt to change eating patterns rather than just focusing on weight loss because this reduction of weight will occur inevitably from the appropriate behavioral change. Patients may wrestle with such considerations as the belief that they "lack willpower" or that there is some inherent personality flaw that makes them the victim of their particular habit. These considerations may make it difficult for them to develop a realistic perspective of what is required to achieve success.[6]

Involving a patient in self-observation by the creation of a comprehensive record of the behavior will help to define it within its various components. A useful method to use requires keeping a diary that elucidates antecedents (cues, stimuli) and consequences.[35] To use the example of smoking, several pieces of information should be recorded. With the date and time of each cigarette that is smoked, one should include the activity that preceded the desire—such as stress, a cup of coffee, completion of a meal—and then the response that was achieved—relaxation, irritation of others, cough—and the moods and thoughts that the patient felt at the time—that is, boredom, anger, "wondering why I am smoking so much." Additionally, a scale of 1 to 3 can be used for each cigarette, with 1 representing the cigarette that one could not do without, 2 for one that is less necessary and 3 for one that could have been avoided altogether. This record can provide patients with insight into the nature of their habits and recognition of opportunities for modification.[36] A similar diary is useful for other life-style-related activities such as eating and drinking. The mere act of keeping such a diary may accrue the additional benefit of some alteration of a patient's behavior toward the desired outcome.[37] The effort involved in recording each cigarette smoked coupled with the fact that a previously relatively automatic activity is now being consciously documented, will usually reduce consumption.

This baseline recording provides the basis for a physician-patient discussion and a meaningful analysis of the habit and the desired outcome. From this base, one can set into action the other steps required to effect behavioral change.

The second step involves realistic goal setting. The patient, with the assistance of a physician, should determine the goals to be achieved, with the steps leading up to their attainment being clearly defined. The definition of these short-term achievements is extremely important, because their accomplishment serves to reinforce the desired behavior. Accompanying these steps and the eventual goal should be appropriate rewards. An example may be that a patient put money that normally would be spent on cigarettes into a jar to be spent after three months' abstinence on some desired luxury. Some short-term rewards can include going out to a movie each week during which more than 2 lb are lost, or going for a 30-minute walk on a day when no cigarettes have been smoked. These provide simple mechanisms for short-term positive reinforcement. Perhaps the most effective compensation is the results of the behavioral change itself. Control of overeating that results in weight loss and a more physically attractive appearance or stopping smoking and developing an exercise program that results in an increase of vitality are their own rewards.

This process can be greatly facilitated by a formal contract. This is a powerful and effective mechanism for helping to ensure behavioral change.[38-40] The components of a contract should include statements of the long-term goals in behavioral terms, rewards and a deadline for accomplishment. The steps required to reach the goals and the rewards to be achieved along the way should also be clearly stated. Reporting and monitoring methods should be delineated as well as where responsibility lies for each of the actions.[41] By explicitly detailing the activities a patient must undergo to fulfill the terms of the contract, a very effective and subtle form of patient education is accomplished. This contract, which should be signed by the patient, serves to formalize a patient's commitment to the program and in so doing reinforces the desired behavioral change. This contract can be renegotiated if it appears that the original goals were unrealistic; however, frequent revisions should be avoided.

By continuing self-recording of a behavior, a patient is provided with a visual reminder of the activity and the progress achieved in its modification. This is, in itself, some reward; however, adding some fun to the process and making it a game rather than a chore can help ensure success.

The reward that accrues when others, including a person's physician, notice the effects of these life-style changes is an important mechanism that maintains motivation. Follow-up visits to a physician should provide an opportunity for enthusiastic support when the desired goals are achieved. Patients should continue to incorporate these new habits into their lives so that the role of physicians can become more peripheral.

Aversion techniques are other behavioral strategies that can result in life-style change. These include rapid smoking methods, faradic stimulation and other procedures that can be used to modify antecedents and consequences. While many of these methods are effective, they will not be discussed here within the context of patient education.

Other Office Strategies

Incorporating patient education into a regular office visit can be facilitated through a variety of methods. Waiting rooms provide an appropriate setting in which patients may begin to develop an understanding of the therapeutic milieu that is being created by the physician. For example, various patient education posters may be displayed. Humorous posters, such as those produced by the American Cancer Society and DOC (Doctors Ought to Care),[42] which parody Madison Avenue prosmoking advertisements, are particularly well received. A notice board in a waiting room can be a way of displaying important information such as health promotion articles from magazines, activities within the community and a variety of other relevant materials.

Waiting room magazines afford an opportunity for physicians to take a moral stance. Providing magazines that do not accept cigarette advertising prevents patients from receiving subliminal counterproductive messages within physicians' premises. Some have advocated a stronger position whereby periodicals are scrutinized for those advertisements that enhance an unhealthy life-style and then, with a felt-tip pen or an appropriate rubber stamp, a disparaging statement is applied such as "This advertisement is a rip-off."[43] A patient education library or an audiovisual room can provide an opportunity for patients to select material of interest or to have some programming scheduled.

The use of a health behavior questionnaire as a part of the patient record data base can be revealing and educational. This can also stimulate dialogue about selected life-style-related activities.

To supplement a physician's advice, handouts can be effective; these should not supplant one-to-one communication, but rather augment the message by offering further clarification of the directions provided and by serving as a record to which a patient can later refer. Unfortunately, many patient education materials are at levels beyond the average person's comprehension.[44] It has been estimated that most persons read at the 7th or 8th grade level whereas most patient education materials are written at 10th through 12th grade levels.[45]

Bibliotherapy, the use of selected well-written books and materials, is an effective and useful adjunct. This provides patients with information in a more comprehensive format than that available in a brief office visit. It also helps to provide insight into a patient's condition and strengthens the impact of the physician's advice.[46]

A patient education newsletter can be an additional method of information transfer. This can reinforce data presented previously and provide further evidence of the physician's commitment to patient education.

Some patients do well with one-on-one counseling whereas others benefit by group support and encouragement.[47] Development of interest groups focusing on weight control, smoking cessation and the like is an activity that physicians may wish to initiate within the context of their office.

Perhaps the most important place where patient education occurs is within the examination room during the doctor-patient interview. The influence of a physician's advice has already been discussed and its impact should not be underestimated.

Community Activities

Physicians should also be aware of other community health education resources. Various public and private organizations provide services in most communities. The offerings may consist of exercise classes, smoking cessation clinics and nutrition education; these can provide a valuable point of referral.

Physicians can also be important agents of social change by virtue of their prominent position in their communities. Speaking engagements at service clubs, high schools and elderly citizens' groups and involvement with the media and local press can provide valuable opportunities for intervention and consciousness-raising. Involvement in other community activities such as health fairs or "fun runs" can furnish other opportunities.

The workplace is a wonderful venue for health education. The American Academy of Family Physicians has recently expanded its activities in this area after a successful pilot study with the International Ladies Garment Workers Union. In this study, employees at several factories were surveyed regarding subject areas in which they would like health information. Family practice residents then went to the work sites and gave lectures followed by audiovisual presentations, concluding with question-and-answer sessions. These presentations have been very well received by workers and have provided information not available through other means. A program has now been developed for expanding this to other industries around the country, with family practice residents and private practitioners as educators.

Reimbursement

The question of payment for patient education is posed as a significant barrier to the provision of these services. A white paper published by Blue Cross and Blue Shield in 1974 recommended that plans support patient education financially through existing health care payment mechanisms.[48] Patient education, therefore, is considered as an integral part of any therapeutic intervention and, for this reason, reimbursement is considered within the regular office visit for the usual illness care.[49]

Embarking on a life-style-modification program and billing for services as such will most likely not be reimbursed by third-party payors. It has been suggested that if billed services and procedures are supported by diagnoses listed in the claim—such as chronic obstructive pulmonary disease or hypertension, rather then smoking-cessation therapy—reimbursement would be provided for a physician's service to the extent that it is covered by a patient's policy.[50]

A study currently in progress is investigating the issue of direct reimbursement for health education. This is the INSURE Project on Life-Cycle Preventive Health Services. This feasibility study, which has significant support from many insurance companies, is analyzing the planning, implementation and evaluation of a wide range of preventive health services including patient education. It is anticipated that the findings from this study will provide some direction regarding the future of reimbursement for patient education and other preventive services.[51,52]

Conclusion

The changing priorities of the public and the health profession regarding the prevention of disease and the maintenance of health demand the sharing of knowledge and skills to form a partnership in health.

Physicians are in a unique position to have an important personal impact on the health of their patients and that of society by fulfilling their teaching role.

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Some Ingredients for Mental Health

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When the body is ailing the mind is soon impaired. Good health practices contribute to longer and better life. A balanced life of work-rest-play is necessary to human health.

Psychosocial stresses at any period of life may impair morale and productivity and increase the likelihood of physical or mental disease. Bereavement, separation, divorce, loss of friendship, retirement, loss of self-esteem and symbolic losses contribute significantly to mental and physical ill health. Social and psychological support systems are vital to mental health maintenance.

Mature persons evolve principles, values, moral and ethical tenets, philosophic and religious ideals and special codes of conduct to give meaning to their lives. The basic needs of survival and procreation must be integrated with moral precepts relating to interindividual behavior so as to give a person a feeling of self-worth, which is an indispensable element in mental health.

(Greenblatt M: Some ingredients for mental health, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:861-863)

I remember vividly that in 1943 Harvard's total commitment to the teaching of undergraduate students in psychiatry, for all four years together, was only 58 hours. Hundreds of hours at that time were devoted to the teaching of medicine or surgery. That year a new Professor of Psychiatry was appointed, Harry C. Solomon, MD. He convinced the powers that be that psychiatry teaching in a modern curriculum should rank in importance with that of medicine and surgery. This finally came to pass.

The first class of students to receive this intensified training was skeptical about its value, as were a number of professors in the biologic sciences. But gradually the hearts and minds of the medical students were won over. Moreover, a point was reached in the late 1940s and early 1950s where medical students in such large numbers were opting for a career in psychiatry that the professors in several other disciplines became "nervous"—their specialty was losing converts to a vague, poorly defined and scientifically underdeveloped area.

The field of mental health theory and practice has, indeed, come a long way. World War II taught us that the incidence of mental casualties on the field of battle was often as great as casualties resulting from physical injuries. Practitioners in medical and surgical fields began to pay more attention to the psychiatric manifestation of somatic disorders, which loomed often as high as 70% of their cases. The discovery of the effectiveness of electrotherapy and then psychopharmacologic agents, plus clinical trials with a number of different interpersonal and social therapies, paved the way to greater acceptance of the field of psychiatry by both the medical profession and the lay public.

One of the notable new trends has been a shift in emphasis from secondary and tertiary prevention to primary prevention—that is, the early detection of risk cases—before clinical disease has manifested, together with the study of appropriate interventions to prevent predictable illness from emerging. Longitudinal epidemiologic studies of healthy and sick populations have shown an impressive number of patient cohorts who are vulnerable to disease but who are receiving insufficient attention. Examples of illness-prone groups of persons (to mention just a few) are young persons reared in families with alcoholic parents; persons from families with affective or schizophrenic disorders; young people joining their peers in experimenting with drugs and in whom social and school adaptations are slipping perilously; elderly persons, especially those living alone without family and friendship supports, and persons who have undergone a series of traumatic events within a short period of time.

The more predisposed members within the risk-prone cohorts that have been followed seem to be persons from lower socioeconomic groups and from minority populations, poorly educated persons living under circumstances of severe poverty and those lacking secure employment or hope for upward mobility in the future.

Another shift of emphasis—or, perhaps more strictly, an expansion of emphasis—has been in the domain of *maintenance* of mental health in existing "healthy" populations,

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including enhancement of happiness and productivity in these normal populations. This is commonly referred to as the area of "positive mental health," the concept being that just as sick people vary in clinical severity of their illnesses, so well people vary in degree of euphoria, satisfaction with life and personal well-being. The goal is to make the most of our days on earth.

There are three areas of concern related to maintaining mental health. They are biologic, psychosocial and existential—the latter is concerned with giving *meaning* to life.

Biologic factors relating to health and mental health are discussed in other papers in this issue. Suffice it to say here that when the body is ailing, the mind is soon impaired. Persons who suffer the ravages of flu often discover how difficult it is to get back on their feet—their spirits flag, energy and drive are impaired and depressed feelings hamper their concentration and productivity. It may take months to return to former equilibrium. Patients with diabetes mellitus may suffer impotence, with attendant anxieties and complications. Patients with arthritis, ulcer disease and cancer all have very difficult adaptations to make both to their illnesses and to the world. Both morale and effective functioning in our stressful, often frenetic, society can be shattered.

Thus, the treatment of physical disease as early and as effectively as possible is highly desirable for, if allowed to develop, physical disorders will inevitably affect mental health.

Breslow and others have shown that good health practices contribute to longer and better life. Thus, we are enjoined to eat breakfast regularly; disdain smoking; take regular, moderate exercise; sleep eight hours a night; maintain a normal weight, and drink moderately.[1-3] Vacations and sports make a great difference in the mental health of many people. Alternating work with rest and work with play are necessary to human health. Recently, running has been touted as an antidote to depression. Music, painting, dancing, gardening and a large variety of other hobbies give interest to life, balance work-a-day stresses and reduce tensions. Each person must seek that configuration of activities that is most personally rewarding.

In the *social-psychological sphere,* we should be alert to the major change periods in our lives and the risks inherent in those periods. In early life these stress periods occur when adapting to school, gaining acceptance into peer groups, relating family values to peer culture, dating and falling in love. Later, one must be alert to stresses of becoming self-supporting through work or profession, marrying, rearing children, becoming a "parent" to failing parents, facing parental disability and death, negotiating personal retirement and adapting to one's own dying.

Significant losses at any time of life impair not only mental health, but also physical health. The most familiar paradigm is loss of a spouse. This is followed by numbness, anger, depression and a host of other mental reactions that are attempts to restore and "resurrect" the lost object. Eventually, in a healthy person social and psychological restitutions take place. However, recent studies emphasize the complexity, variety and long duration of psychological symptoms of loss, as well as effects of serious loss on physical health. Bereaved persons suffer far more illnesses for some time after a loss than do persons who have not lost a loved one. They visit physicians and are admitted to hospital more, use more drugs and their death rate is significantly higher than normal.

Losses may be other than those related to death of a loved one. Separation; divorce; loss of friendships, of status and prestige, of a familiar environment and of self-esteem, and symbolic losses contribute significantly to ill health. Rahe and colleagues[4] have shown that a variety of life event changes may take their toll on individual health, particularly if a number of these changes are concentrated within a short period of time.

It is said that "Friends are good medicine." Recent studies using the concept of social networks emphasize that healthy people enjoy far more support from family and friends and other social contacts than do persons who have succumbed to disease. These social networks operate by mobilizing the emotional and adaptive resources of a person, enabling him or her to master emotional burdens. Network members share tasks and provide money, materials, tools, skills, guidance in problem solving and love and affection. They satisfy a person's need to be dependent and to be depended on and to control and be controlled, and they satisfy the primeval yearning of all of us to belong. The task panel of President Carter's Commission on Mental Health, after much study, concluded that community mental health could be enhanced by strengthening the natural networks to which people belong and on which they depend.[5]

A nuclear family is most influential in providing emotional support. Unemployed men, for example, who had the emotional support of their wives had fewer emotional and physical symptoms of illness than unemployed men without such support.

Studies of psychiatric disturbances among women show that those women who have an intimate, confiding relationship with a husband or boyfriend are more protected against symptoms of psychiatric illness than those who are bereft. Persons with confidants are more able to survive traumatic social losses. Support systems are strategically helpful not only in understanding the mental health of normal people, especially during trying times, but mentally ill persons, too, are greatly assisted in recovery if support systems are adequate.

Methods using social network theory to improve the quality and quantity of social interactions of mentally ill persons, both within institutions and in the community, have been practiced in the past under the rubrics of "environmental manipulation," "social therapy," "humane engineering" and so forth. In the future we may expect many more conscientious efforts in this sphere, and more demonstration research aimed to be helpful to practitioners. The implications of social networks for the health of young people who are susceptible to peer pressures and the need for group acceptance are known to all parents. Grownups will normally be active in many social groups; however, they should be aware of, and resist, the tendency for a constriction of their social spheres in later life, as friends fall away, job tenure ends and physical energies decline.

Society must take a hand in this problem and, indeed, many innovative programs have been established in both the public and private sectors. For example, in Sweden, persons who deliver mail check on elderly folks who may be isolated. In the United States we have programs for senior citizens, for

spouses who have lost partners and for senior persons who are looking for a new opportunity for service. In this last category is the strikingly successful federal volunteer program in which senior citizens adopt retarded patients as surrogate children. Volunteering is a strong motif in our American society, and one is impressed by the number of volunteer services in state and Veterans Administration mental hospitals, where interaction with sick persons functions as a health-enhancing mechanism for both parties.

Silverman is largely responsible for showing that widows in acute mourning may be helped greatly by widows who have traversed the mourning period and successfully rehabilitated themselves.[6,7] Without much professional supervision, successful widows help a new widow to mourn, to manage her affairs, contact members of her network and reach out to new people. This modality has been applied in numerous situations in which persons sharing the same life situation meet, discuss common problems and support each other emotionally. Parents of abused children, divorced parents with children and parents of emotionally disturbed children have in many instances profited greatly by these contacts.

Persons must determine for themselves what is a properly "balanced life." In some instances it may be wise to seek intelligent counsel, especially someone who has known the person for a long time. A decision as to the best life-style and proper balance of activities must take into account such variables as genetic vulnerability, sources of gratification and of distress, available alternatives, coping strategies and the goals and meaning of a person's life.

Early awareness of disturbance of equanimity, joie de vivre and effectiveness in occupation should be cultivated. This is particularly important in maintaining the health of persons who have recovered from illness, but who are still vulnerable. For example, those who have recovered from depressive disorders should consider carefully the meaning of sleeplessness, irritability, difficulty concentrating, psychomotor retardation and generalized anhedonia, for these symptoms may herald a new attack. It may then be wise to see a skilled professional with whom a careful review of life events, chronic tensions, actual or symbolic losses and changes in important interpersonal relationships may be made. A change in life-style, a rebalancing of the work-play-rest equilibrium or a slight readjustment in drug dosage schedule may be all that is needed.

Persons susceptible to schizophrenic-type illnesses may manifest such warning symptoms as withdrawal and distancing from others, inactivity or overactivity, excessive preoccupation with internal content, bizarre behavior or verbal expressions, impulsive attempts at repair of interpersonal, social or occupational relationships or a combination of all of these.

Finally, consider *existential factors.* Each person throughout life organizes his or her behavior, conscious or unconscious, around a set of values, beliefs, codes of conduct, moral tenets, ethical precepts, religious teachings or philosophical ideals. The glory of human evolution from animal ancestors is that human beings are impelled to think consciously of how to live with others. The aggressive, defensive and destructive drives of humans have evolved out of eons of necessity for survival in a savage world. The more considerate, loving, peaceful motivations arise out of the fact that humans are by nature gregarious. They are dependent on their fellow beings and some of their deepest urges are for procreation and the survival of the species. At the interface between those two great forces—procreation and survival of the species, on the one hand, and individual survival and well-being on the other—are ethics, morality, religion and philosophy.

As we grow up we are acculturated by our parents and significant others. We learn more or less successfully to deal with authority and competition, to master a field of information and to learn a trade or profession so as to become relatively independent. We learn the rules of the game in approaching the opposite sex and how to be a member of a family or belong to a group. In our youthful games we gain experience in winning and losing; as adults we compete for a place in the sun and pursue gratifications while striving to satisfy our imperious physical needs. Many gain great comfort from religious or philosophical beliefs. Whatever path is chosen, human life must at all events have meaning. Meaning is an indispensable component in humans of a sense of self-worth; the sense of self-worth in turn functions like a critical "organ" in our bodies; its proper maintenance makes mental health possible.

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Healthy Exercise

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Persons at any age can substantially improve their fitness for work and play through appropriate exercise training. Considerable evidence indicates that physical activity is valuable for weight control, modifying lipids and improving carbohydrate tolerance. Less rigorous scientific data are available for associated long-term blood pressure and psychological changes with habitual exercise. Strenuous physical activity most likely reduces the incidence of coronary heart disease and the detrimental impact of certain chronic diseases on health. Adverse effects may result from a training program, but the major concern is the susceptibility to cardiovascular events during and immediately after exertion. To achieve optimal benefits with minimal risk, exercise must be carefully prescribed within the context of overall health and training objectives. Taken altogether, a distinct rationale exists for regular vigorous exercise as an integral part of a personal health maintenance program.

(Oberman A: Healthy exercise, *In* Personal health maintenance [Special Issue]. West J Med 1984 Dec; 141:864-871)

More and more people are turning to exercise to insure long-term health. Prestigious health organizations, including the World Health Organization, the American Heart Association, the Public Health Service and the American College of Sports Medicine, have endorsed the concept.[1-4] Working parties of the Royal College of Physicians of London have recommended adoption of a more physically active life-style to reduce the prevalence of coronary heart disease and obesity.[5]

New information has dispelled many of the myths and dogmas associated with training for athletic competition. These data indicate many potentially beneficial physiologic adaptations, but until further clarification of these changes can be obtained, the evidence and control for disease prevention must be mainly inferential.[5-7] Numerous unanswered questions persist on the long-term effects of vigorous exercise, including possible hazards. How much and what kinds of exercise are needed require further investigation to provide appropriate exercise plans for persons at different ages and different levels of health. Nevertheless, it seems likely that regular physical activity is desirable for personal health maintenance and probably reduces the impact of certain chronic diseases.

Generally, the medical community has not kept pace with the growing public awareness of exercise as a health measure. Persons want assistance from their physicians on the therapeutic value of exercise, the kinds of exercise required to obtain health benefits and the necessary evaluations before embarking on an exercise program. Numerous fitness centers and health spas that have sprung up in response to this desire for exercise attempt to fill this void in health counseling. However, exercise must be carefully prescribed within the context of a patient's health. It is important for physicians to familiarize themselves with the physiologic and psychologic consequences of exercise training so that they can best inform patients.

General Health Benefits

Physical activity provides the stimulus required to maintain the structural and functional integrity of the cardiovascular system, the musculoskeletal system and probably the autonomic nervous system and motor neurons.[6-8] With an appropriate exercise schedule, adaptive responses will determine a person's capacity to meet exertional stress. Depending on the exercise routine, an array of other health advantages can accrue over a period of months.

Most Americans get little strenuous exercise at work, or even during leisure hours, at least not enough to induce the metabolic adaptations associated with exercise training. There is no way to achieve physical fitness and the desired adaptations other than through regular physical activity. Healthy persons and patients who have chronic diseases, in-

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ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
Vo_{2max} = oxygen consumption during maximal exercise

cluding coronary heart disease (CHD), can substantially increase their levels of fitness at all ages to attain maximal functional capabilities. Also, habitual exercise can minimize the secular functional impairment beginning after the second decade of life. Aerobic capacity declines with advancing age twice as rapidly in sedentary men as in physically active men.[9]

Components of Fitness

Because the nature of the training determines the specific adaptations that occur, an exercise program should address the major components of fitness: cardiorespiratory endurance, flexibility and strength.

Cardiorespiratory Endurance

Dynamic or endurance-type exercise, commonly termed aerobic exercise, increases aerobic capacity of exercising skeletal muscle in proportion to the muscle mass used and the intensity of exertion.[9] Oxygen consumption during maximal dynamic exercise (Vo_{2max}) determines aerobic functional capacity and is defined as the product of cardiac output and arteriovenous oxygen differences. Functional limits are determined primarily by the adaptive responses in the cardiovascular system leading to enhanced transport of oxygen, carbon dioxide and heat.

Cardiorespiratory endurance activities involve rhythmic activity of large muscle groups, such as those used in brisk walking, jogging or swimming. An exercise session conducted at 60% to 80% of the Vo_{2max}, corresponding to about 70% to 85% of the maximal heart rate for a 20- to 40-minute period, three to four times a week, will bring about the desired adaptations.[7,10,11] Less strenuous levels of exercise may be sustained for hours, but, though useful for weight reduction and psychological benefits, are usually insufficient to confer optimal levels of fitness on most persons. Whereas more exhaustive "workouts" may be essential for achieving peak athletic performance, such an approach may actually be detrimental for maintaining health and preventing disease because of the associated hazards. By raising the maximal capacity, the submaximal oxygen requirements of daily living should not lead to undue fatigue and dyspnea (Figure 1). Assuming symptoms develop when a person exceeds 75% or more of maximal capacity, a 40-year-old man with low fitness of 24 ml of oxygen per kg of body weight per minute will have symptoms at an 8-km (5-mile) per hour walk-jog requiring 30 ml O_2 per kg per minute until he increases his maximal capacity to 40 ml per kg per minute, at which point he becomes asymptomatic. Alternatively, he could reduce his speed to 5 to 6 km (3 to 4 miles) per hour rather than exercise to improve fitness so that the exertional level would not exceed the 75% threshold. Healthy 50-year-old men who train regularly can achieve a Vo_{2max} 20% to 30% higher than that of younger, sedentary men.[6] Increments in functional capacity may be especially important for older persons who may be starting from a very low level of fitness. Such improvements can result in almost complete self-care and independence.

Flexibility

Flexibility can best be obtained by stretching exercises that result in improved suppleness and neuromuscular coordination. These activities are valuable for overall fitness and

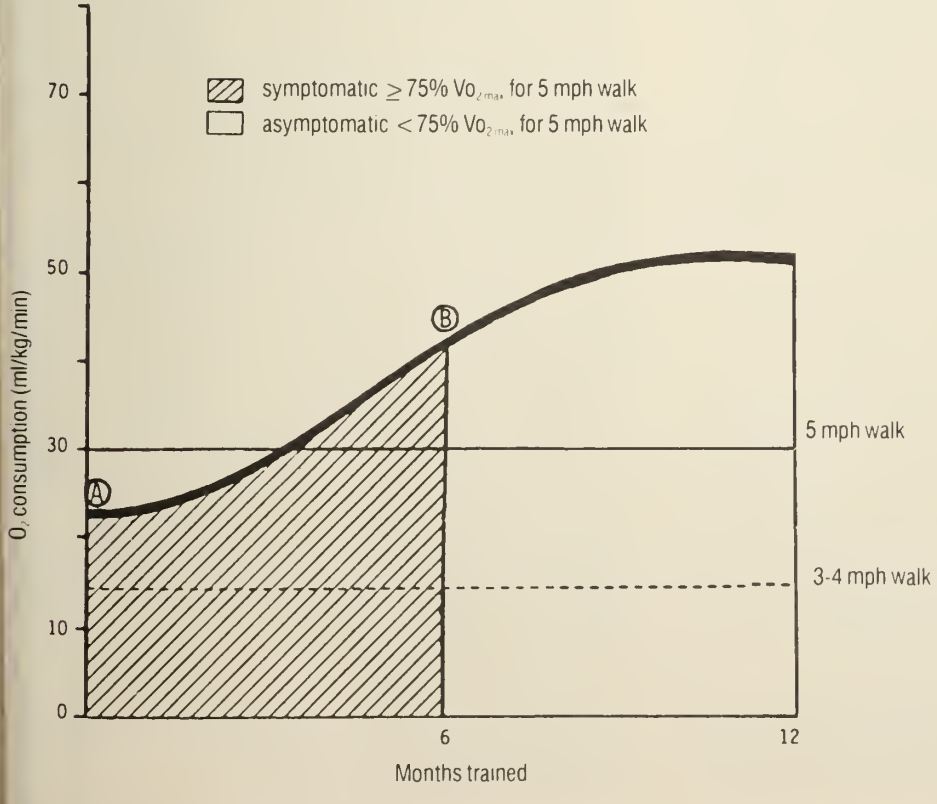

Figure 1.—Assuming symptoms such as undue fatigue and dyspnea develop when a man exceeds 75% or more of his maximal capacity, this figure shows that a 40-year-old man with low fitness of 24 ml of oxygen per kg of body weight per minute (point A) will have symptoms at a five-mile-per-hour (mph) walk-jog requiring 30 ml O_2 per kg a minute until he increases his maximal capacity to 40 ml per kg per minute (point B), at which point he becomes asymptomatic. Alternatively, he could reduce his speed to three to four miles per hour, rather than exercise so that the exertional level would not exceed the 75% threshold. Vo_{2max} = oxygen consumption during maximal dynamic exercise

muscle tone, thus indirectly contributing to feeling better and facilitating specific physical activities encountered in jobs or hobbies.

Strength

Strength training involves working muscle groups with progressive resistance overloading, which results in increased muscular strength. Strength is maintained by completing several sets of repetitive muscular contractions with work loads of 1 to 4.5 kg (2 to 10 lbs). Most of these contractions are a mixture of isotonic (a constant resistance moved through a range of motion of the involved joint, such as lifting a weight) and isometric (no change in angle of involved joint, with little or no change in length of contracting muscle, such as pushing palms of hands together) maneuvers. Isometric contractions may be less irritating to a painful joint or soft tissue injury, but tend to produce pronounced elevations of blood pressure, thus inordinately increasing the work load on the heart.[12]

Specific Metabolic Benefits

Maintenance of optimal body weight and composition and favorable changes in carbohydrate and lipid metabolism through regular exercise have been well documented.

Body Composition and Weight Control

The value of exercise for reducing weight is grossly underestimated, as most people associate weight loss with dieting rather than with exercise. Exercise conditioning has been shown to reduce body weight and adiposity by increasing energy expenditure, raising resting metabolic rates, accelerating mobilization of fat stores and increasing the likelihood of changes in eating patterns.[7,8,13]

Physically active persons, such as those running several miles per day, consume up to 15% more calories a day than their sedentary counterparts, yet remain significantly leaner. Weight gain or loss reflects small changes in food intake or exercise over a long period of time. Most recent data show little change in food intake with moderate exercise, and short-term suppression of appetite with more vigorous exercise. Furthermore, exercise counters the autoregulatory decrease of basal metabolic rate with reduced caloric intake by increasing the metabolic rate for several hours, accelerating caloric expenditure and facilitating weight loss.[13] This elevated metabolic rate becomes particularly important if the exercise occurs regularly and frequently over a long period of time.

It has become increasingly apparent that effective long-term weight control requires a balance of energy intake (food) and energy output (exercise). The calories required each day can be estimated by multiplying the weight of a person by the number of calories per kilogram (or pound) for usual activity levels (Table 1). A 68-kg (150-lb) woman engaging in moderate activity requires 2,100 calories per day (150 lbs × 14 calories per lb = 2,100 calories). To lose 1 lb per week, she must reduce 500 calories a day (3,500 calories per week), either by cutting back on intake, by increasing activity or by some combination of the two.

Other advantages obtained through exercise include the relatively greater loss of body fat compared with muscle and bone tissue. Fat is preferentially used for energy needs. After about 20 minutes of exercise, the body relies increasingly on fat for energy, mobilizing undesired fat deposits.[13] Thus, exercise results in more muscle and less fat even if overall weight is not altered.

TABLE 1.—*Calories Needed Daily for Each Pound of Weight*

Activity Level	*Calories per Pound*	
	Women	*Men*
Very light (sitting mostly)	12	14
Light	13	15
Moderate (housework, gardening) .	14	16
Strenuous	15	17
Very strenuous	16	18

Carbohydrates

Less insulin is secreted in the trained state. However, glucose tolerance changes little, or even improves. Physical training mediates this favorable adaptation through at least three separate mechanisms: increased sensitivity of insulin receptors; depletion of muscle and liver glycogen, creating available glucose storage space, and enhanced muscle cell permeability to glucose.[14] Although a single bout of exercise can greatly influence the insulin response to a carbohydrate load, the effects are not as great as the cumulative response to habitual vigorous exercise. Short-term muscular activities that produce these metabolic changes in carbohydrate metabolism do not persist with prolonged periods of inactivity.[14] This reduction in insulin may have an effect on the development of coronary heart disease. Apart from its role in carbohydrate metabolism, insulin has been postulated to be independently atherogenic.[15]

Lipids

Exercise training consistently raises levels of high-density-lipoprotein cholesterol. This lipid subfraction is inversely related to CHD and is important for predicting the development of CHD.[16] Other advantageous changes are a fall in low-density-lipoprotein cholesterol level, a rise in apolipoprotein A1 level and an increase in lipoprotein lipase content.[17] The effect of exercise on total serum cholesterol remains controversial. Exercise reduces triglyceride levels, presumably through the lipoprotein lipase changes, and, as with carbohydrate metabolism, the effects depend on both acute exercise activities and long-term training.[18] Seasonal variations in lipids, concomitant weight and dietary changes and lack of true control groups complicate interpretation of the studies of lipid modification with exercise. Another unresolved consideration is the question of the exercise threshold for lipid changes. In recent studies favorable lipoprotein changes were confined to those who had either been running for at least four years, or had been running 56 km (35 miles) or more per week,[19] those who averaged at least 20 km (12.4 miles) per week of running[20] or those who ran at least 13 km (8 miles) per week for one year.[21] The concept of an exercise threshold for lipid changes is consistent with observations that more vigorous forms of exercise are required for reducing the risk of coronary heart disease.

Psychological Benefits

From available research, mainly correlational studies, the conclusion is generally made that exercise is associated with an improved affect and self-concept, especially in persons

who are moderately depressed or anxious.[22,23] Claims have also been made that exercise bolsters cognitive performance during or after stress.[24] Patients with mild to moderate depression often respond poorly to drugs and tend to do well with the mood-enhancing effects of an exercise program.[8,23] "Feeling better" has been almost universally claimed as an accepted benefit of exercise, while others report that exercise enables persons to handle stress better.[8,24] Also, some investigators have claimed that exercise can modify personality type and thus indirectly reduce susceptibility to stress-induced disorders.[25] However, the general belief that exercise results in improved health habits has never been subjected to rigorous scientific scrutiny.

Current emphasis on neurohumoral control of stress concerns the influence of submaximal exercise on circulating catecholamines and endorphins, and the anecdotal evidence of a "high" with exercise. Training tends to enhance parasympathetic activity and reduce the response of catecholamines to exercise. The perception of effort during exercise has also been directly related to circulating catecholamines.[26] Current work indicates that endogenous opiates stimulated by exercise dampen the release of catecholamines and consequently appear to be important modulators of neuroendocrine responses to stress.

Specific Disorders

Coronary Heart Disease

Despite the decline in cardiovascular mortality over the past decade, CHD remains the leading cause of death and disability in this country. For those reasons alone, any personal health maintenance program should be strongly oriented toward preventing CHD and its complications. Whether or not physical activity protects against CHD has been widely debated.[6,7,27] Population studies consistently showed significantly lower mortality rates in physically active workers compared with sedentary workers.[28] However, the design of such studies did not permit a clear distinction between protection by exercise, or selection of healthier persons by virtue of their continuing to be physically active at work. Taking possible selection factors into account, a study of longshoremen showed 49% less coronary events for those who expended 5 to 8 kcal per minute of energy at work, as compared with their less active co-workers.[29] Data from more recent incidence studies with less potential for bias have now accumulated (Table 2). Analysis of CHD morbidity and mortality among Harvard alumni observed for ten years or more, expending 2,000 or more kcal per week in exercise, showed a threshold above which there was a significant 50% reduction of myocardial infarctions and sudden death in men, as compared with those expending less per week.[30,31] Contemporary physical activities of the alumni outweighed any influence from earlier participation in sports and athletics. Others have found, however, that exercise responses in youth, presumably an index of fitness, significantly relates to risk factors for CHD at middle age.[32] In a prospective study of nearly 3,000 healthy men, but with at least two of the major risk factors, the adjusted relative risk for those below the median in physical work capacity was 6.6, suggesting that poor physical fitness, when accompanied by other major risk factors, enhanced susceptibility to CHD.[33] Several prospective studies have reported a definite relationship between low physical activity and cardiovascular disease and death, while controlling for other prognostic factors. The Framingham study showed an inverse correlation between physical activity and cardiovascular morbidity and mortality, but only one of modest magnitude and only in men.[34] In a study of British civil servants designed to determine the role of exercise in preventing CHD, physical activity significantly reduced both the incidence of fatal coronary disease and combined fatal and nonfatal incidence rates at all ages, especially at older ages.[35] In Finland low physical activity at work increased the likelihood of cardiovascular problems and at leisure time decreased the risk of death.[35a] Data from the Puerto Rican Heart Study convincingly showed physical inactivity being second only to hypertension as the major risk factor for CHD in that population.[36]

TABLE 2.—*Recent Findings From Major Studies on Exercise and Coronary Heart Disease*

Population and Observation Years	*Number*	*Comparison*	*Conclusion*
Harvard alumni 1962-1972, Paffenbarger et al[30,31]	16,934	Reported energy expenditure	Risk of first heart attack was inversely related to energy expenditure in adult life, independent of other influences on heart attack risk.
The Framingham Study, 1957-1971, Kannel & Sorlie[34]	4,220	Physical activity index	Cardiovascular mortality and morbidity were inversely related to physical activity only in men; this relationship was significant and independent of other major risk factors, but the effect was modest in comparison.
British civil servants, 1969-1978, Morris et al[35]	17,944	Leisure activity; questionnaire	The coronary heart disease rates of men who took vigorous exercise were lower for both fatal and nonfatal events; these findings were most striking in older men.
North Karelia and Kuopio (Finland), 1972-1978, Salonen et al[35a]	6,665	Reported physical activity at work and leisure	Low physical activity at work was associated with increased risk of acute myocardial infarction, cerebral stroke and death from any cause in men and women, controlling for age and other risk factors; leisure-time physical activity related only to a decreased risk of death.
Puerto Rico Heart Health Program, 1965-1973, Garcia-Palmieri et al[36]	8,793	Physical activity index	The physical activity index was inversely correlated to the known coronary risk factors; multivariate analyses indicated a significant, independent inverse relationship between exercise and the incidence of coronary heart disease: physical activity appeared to be a separate protective factor against heart attack.

TABLE 3.—*Secondary Prevention With Physical Training in Previous Randomized Controlled Trials*

*Trials**	*Number*	*Intervention*	*Follow-up (months)*	*Mortality (%)*		*Nonfatal MI (%)*	
				Control	*Exercise*	*Control*	*Exercise*
Sweden (1968-1972)	315	Supervised exercise 3 ×/week	48	22.3	17.7	17.9	15.7
Finland (1969-1972)	298	Supervised exercise 2-3 ×/week	12	21.9	17.1	5.4	8.1
Finland (1969-1972)	380	Daily home exercise	29	14.0	10.0	11.2	18.1
Canada (1972-1978)	733	Partially supervised exercise 2-4 ×/week	48	7.3	9.5	9.3	10.3
United States (1974-1979)	651	Supervised exercise 3 ×/week	36	7.3	4.6	3.3	4.6

MI = myocardial infarction

*From Oberman[11] and May et al.[44]

In reports from these large-scale studies, the energy expenditure necessary for protection is estimated to be about 7.5 kcal per minute for exercise sessions. Such levels correspond to brisk walking, jogging at 8 km (5 miles) per hour, heavy gardening or bicycling at 16 km (10 miles) per hour. This effect of sustained physical activity may emanate in part from its influence on some of the risk factors that play major roles in the development of atherosclerosis. However, the impact of vigorous exercise appears to be independent of the major cardiovascular risk factors and somewhat less powerful.[37]

Habitual strenuous exercise may augment myocardial blood supply. In longitudinal studies, coronary flow patterns changed early after the onset of a training program, which indicates that regulatory adaptations are taking place.[12] Experimental evidence also exists for a training-induced increase in the size of the coronary vascular bed, even though multiple studies have failed to show an increase in collateralization in the absence of coronary lesions in humans.[11,12] Patients may better tolerate thrombotic stimuli after training. In hypercoagulable states, the fibrinolytic response to various stimuli may be enhanced in trained persons[8,11]; further work is required to clarify changes in platelet activity.[8] Also, a decreased propensity toward arrhythmias may be a product of long-term training.[38] In this experimental study daily exercise modified cardiac electrostability and autonomic control of heart rate in such a way as to decrease vulnerability to life-threatening dysrhythmias. Reduced sympathetic tone after conditioning may reduce serious dysrhythmias; however, hygienic intervention trials failed to suppress stress-induced ventricular ectopic rhythms in healthy men having frequent premature ventricular beats.[17]

Cardiac rehabilitation programs have demonstrated their influence on morbidity in the broad sense as evidenced by reducing symptoms through suitable training for angina patients, post-myocardial infarction patients or patients who have had coronary artery bypass grafting. Such patients can increase their maximal oxygen uptake by 20% or more, alleviating symptoms associated with exertion.[11] The improved functional capacity is due mainly to the adaptations in the peripheral muscles rather than directly in the myocardium or myocardial oxygen delivery.[12,37] The issue of whether myocardial oxygen consumption is enhanced remains controversial. Some studies show an increase with the angina threshold as measured by the rate-pressure product, presumably representing enhanced myocardial oxygen delivery. Others clearly show an increase in the rate-pressure product and infer increased oxygen delivery to the myocardium.[39] The fact that trained cardiac patients can maintain the same pace as many normal persons, however, may be due to physiologic changes other than in maximal capacity. Coyle and co-workers[40] showed that patients with coronary heart disease can maintain a high lactate threshold relative to maximal oxygen consumption, enabling them to exercise at near-maximal levels.

One explanation for the lack of myocardial adaptations has been the limited intensity and duration of most exercise programs. Ehsani and colleagues[41] have found an increased rate-pressure product in patients with coronary artery disease who are on an exercise program of four times per week to levels of 90% maximum over a period of six months to a year. They and others have postulated that the skeletal and autonomic nervous system adaptations occur within weeks but the myocardial changes, only with more intense exertional levels, occur over a period of months.[11]

Exercise training in patients with coronary heart disease appears to be more effective for secondary prevention in those with reasonable left ventricular function.[11] The left ventricular ejection fraction during exercise may be improved after exercise conditioning, probably by the lower heart rate at comparable work loads after training, though the favorable changes in loading conditions of the heart and an increase in myocardial contractility are alternative explanations.[42] Exercise intolerance in patients with congestive heart failure may be due to impaired nutritive flow to skeletal muscles with resultant muscular fatigue.[43]

Early studies of the effect of exercise on recurrent myocardial infarction and death in those with overt CHD were largely uncontrolled, but they clearly established the safety of a supervised training program. Over the past ten years at least five clinical trials on the role of exercise in reducing the reinfarction rate and mortality have been carried out.[11,44] This second generation of randomized, controlled trials disclosed no significant differences in the recurrence of nonfatal myocardial infarctions (Table 3). Yet, with the exception of the study from Canada, all of these investigations with follow-up extending from 12 to 48 months found reductions in mortality of from 21% to 37% in those exercising at an effective level.[11] May and associates[44] justified pooling these data on the basis of the similarity of the studies and because no single study had enough subjects to truly test the exercise hypothesis. Combined analyses from these studies indicate a 19% reduction in mortality ($P < .05$) and suggest that exercise influences the course of patients who have CHD.

Hypertension

Population studies show an inverse correlation between physical activity and blood pressure levels.[8,45] A consistent finding is the lowering of blood pressure at submaximal exercise as might be expected from raising the maximal capacity,

so that any submaximal exertional level represents a smaller proportion of maximal capacity and a lessened physiologic stimulus for heart rate and blood pressure changes (Figure 1). However, the increase in blood pressure from rest to exercise is similar before and after training, suggesting no change in the regulation of blood pressure during submaximal exercise in patients with hypertension.[45]

In several studies endurance training has been more effective in lowering blood pressure at rest in patients with borderline or essential hypertension.[8,39] Generally, these studies have not included control groups, have not assessed simultaneous nutritional changes, have involved small numbers of middle-aged men for only short durations and have varied widely in methods of measuring blood pressure and types of training programs. Evidence at present appears inadequate to recommend exercise training as a form of nonpharmacologic treatment of hypertension.[45] In their 1984 report, the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure suggested that exercise is useful for weight control and may be helpful in reducing blood pressure for those with uncomplicated hypertension.[46]

Diabetes Mellitus

Because its glucose-lowering effect is largely independent of insulin secretion, physical training can be useful in the management of cases of diabetes mellitus. However, moderate exercise alone appears to be ineffective as therapy for non-insulin-dependent diabetes mellitus and cannot subserve the other actions of insulin in juvenile-onset diabetes.[47] In addition, precautions are advised for exercising middle-aged persons who have diabetes mellitus because of the possibility of exercise-induced hypoglycemia and their vulnerability for coronary events.

Musculoskeletal Disorders

Localized osteoporosis develops several months after a limb is immobilized. With vigorous exercise, the mineral content of exercising limbs substantially increases, and it is postulated that exercise can be used to increase the strength of the skeleton and possibly retard the changes associated with inactivity and age. Calcium loss from the os calcis was minimized during weightlessness experienced during space flights by repeated applications of force to the bone through muscle contractions.[48] Regular exercise may also reduce the loss of calcium by postmenopausal women.[7] A cross-sectional survey of postmenopausal women showed that the level of habitual physical activity correlated with bone mass as measured by computed tomographic scanning. Yet, women with exercise-induced amenorrhea have decreased vertebral mineral content.[49] Bone mineral content has been increased in several studies of older adults in exercise programs. This supports the concept that older adults can reduce the loss of bone mineral content that occurs through unnecessary bed rest or immobilization.[7,8]

Studies on the effectiveness of both dynamic and isometric exercise toward improving the function of patients with rheumatoid arthritis have indicated some improvement without adverse effects.[50-52] Isometric exercises have been preferred because of the expected aggravation of joint pain and inflammation with dynamic exercise. Yet, patients with ankylosing spondylitis have reported diminished pain and joint stiffness after dynamic physical training.[48] Well-controlled studies are noticeably lacking, but available data indicate that under careful supervision, patients with arthritis may be encouraged to participate more fully in exertional activities. Muscle weakness, a common clinical problem in the presence of joint disease, might be alleviated without damaging joints further through the judicious use of exercise.

No body of experimental evidence exists showing the efficacy of exercise in preventing or treating low back pain. The premise is based on the knowledge that abdominal and costal muscles relieve the stress on the lumbar spine when lifting and carrying heavy objects.[48] When lifting correctly, the quadriceps effectively distribute weight. Thus, it reasonably follows that strengthening of the abdominal, costal and quadriceps muscles will relieve the load on the lumbar spine and contribute to the relief of low back pain.

Other

Several reports have now shown that progressive exercise is surprisingly effective in managing chronic obstructive lung disease.[7,8,53] Benefits ascribed to physical activity relate to reducing the fatiguability of the respiratory muscles, reversing the effects of inactivity and increasing psychological tolerance of breathlessness. Whereas patients feel better, it is uncertain whether this has any effect on the ultimate course of the disease process. Physical activity has surprisingly little effect on pulmonary function in normal persons.[12] Participation by such patients in training programs is reputedly poor, possibly because of the difficulty in carrying out exercise without supplemental oxygen or the lack of a specific event, as with patients who have had a coronary event, to provoke their interest.[53]

A regular walking exercise may prove of great benefit to patients who have intermittent claudication. Exercising to the point of claudication over a period of time can presumably lead to an increase in calf muscle blood flow during submaximal work.[8]

Physical activity may play a previously unrecognized role in preventing colon cancer.[54] Men with sedentary jobs had a colon cancer risk of 1.6 times that of men whose jobs required a high level of activity, with a stepwise increase in risk as activity level decreased. A proposed physiologic explanation for these observations is that physical activity stimulates colon peristalsis and decreases random, nonpropulsive segmentation activity, thus decreasing the contact time for possible carcinogens. On the other hand, it has been theoretically postulated that exercise training predisposes to the development of cancer.[6] Conceivably, large increases in Vo_{2max} associated with strenuous exercise training accelerate the aging process by increasing the rate of tissue damage by free radicals formed from the oxygen.

Hazards of Exercise

Not to be ignored are the possible risks from exercising. Foremost among the problems of physical activity are those related to the musculoskeletal system; strains to vulnerable areas have been well documented.[8,48] In endurance activities involving the dynamic use of large muscle groups, the muscles and structures to which they attach may become seriously stressed and injured.

Other possible complications of a training program include a variety of reported disorders. Extremes of temperature may predispose to heat exhaustion or heat stroke in unusually warm weather and nonenvironmentally controlled facilities. In cold weather frostbite of extremities and exposed parts of the body is possible. More unusual problems associated with vigorous exertion are hypersensitivity reactions.[55] In some people who have a strong family history of allergies, wheezing, asthmatic attacks or urticaria may develop during or after exercising. Although relatively rare, such episodes can be life-threatening. Little information is available on hormonal changes, especially among men, but lowered testosterone and prolactin levels parallel the changes noted in women runners.[56] Other reported complications include gross hematuria[57] and gastrointestinal bleeding.[58] Experimental evidence suggests that exercise during a viral infection may precipitate subclinical myocarditis.[48] Rhabdomyolysis has been reported as a complication of extremely strenuous exercise and may lead to renal failure.[8]

Much more serious complications arise from an increased susceptibility to cardiovascular events during exertion and immediately afterwards. There are no data to suggest that even strenuous training exercise can harm a "normal" heart, even though training adaptations mimic pathologic findings and may have long-term implications.[8] But in the presence of coronary atherosclerosis, a stressed myocardium may become ischemic and vulnerable to infarction or lethal arrhythmias. Persons dying suddenly of CHD during exertion usually have advanced atherosclerosis regardless of whether or not they were asymptomatic.[59] In a Finnish study, 4.5% of sudden cardiac deaths were related to strenuous or unusual physical activity, usually cardiac arrhythmias due to CHD.[17]

Overall, the acute cardiac risk of vigorous activity has been estimated in several studies and is generally thought to be low.[60] It has been estimated that the hourly CHD mortality increased seven times during jogging, although the absolute death rate of one death per 396,000 jogging hours mitigates against any undue danger.[61] The investigators felt that, due to the rarity of exercise deaths, routine exercise testing in healthy persons at low risk is not justified. Nevertheless, it is not unreasonable to assume that strenuous activity, especially in intemperate weather, can precipitate coronary events in vulnerable persons. Unfortunately, this propensity towards sudden death or infarction with physical activity cannot be predicted with an adequate degree of certainty.[48,60] Consequently, the recommended screening procedure before exercise training for asymptomatic middle-aged men is unresolved. The National Institutes of Health[10] recommend that a graduated exercise program can be initiated without seeing a physician if there is (1) no history of heart trouble, heart murmur, heart attack, hypertension, arthritis or diabetes, (2) no family history of premature coronary artery disease and (3) no exercise-related breathlessness, faintness, dizziness or pain or pressure of the chest, neck, shoulder or arm. The American College of Sports Medicine recommends an exercise test as part of medical screening before a strenuous exercise program for sedentary people 35 years of age or older and younger people at high risk.[4] Guidelines for implementing exercise programs for persons with or without cardiac history wishing to improve their fitness abound in the literature.[7,8,62]

Conclusion

The human body requires exercise to function satisfactorily. Persons at any age can substantially improve their fitness for work and play through appropriate exercise training. Considerable evidence exists for favorable changes in body composition, lipids and carbohydrate tolerance. Blood pressure levels, especially during submaximal efforts, probably can be reduced, but adequate clinical trials are needed. Extensive but nonconclusive data have documented psychological benefits accruing from physical activity. The often-stated belief for associated changes in health habits with exercise has little basis. A variety of other physiologic claims have been reported, not all of which may be corroborated, and some of which may actually be detrimental to one's health. Yet, exercise most likely reduces the incidence of CHD and appears to be a useful adjunct in managing patients who have coronary artery disease, diabetes mellitus, pulmonary disorders and musculoskeletal problems. The risks from long-term training must be taken into account but are not appreciable and are almost negligible in healthy persons.

Taken altogether, a distinct rationale exists for exercise training to maintain health. As with any therapeutic or preventive measure, the benefits and risks for a given objective must be carefully assessed. It is not surprising that exercise is viewed as being so important because of the anticipated changes in physical capacity, appearance and general health. Patients rely on physicians' recommendations, but many practitioners seem reluctant to incorporate exercise into their therapeutic armamentarium. Practicing physicians must take a more active role in prescribing conditioning regimens for those wishing to incorporate exercise into their personal health maintenance program.

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Diet and Health

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The role of diet in personal health maintenance is important whether a person is trying to stay healthy or to treat diet-related diseases such as hypercholesterolemia, hypertension, diabetes mellitus or obesity. Dietary recommendations include limiting fat to 30% and protein to 20% of total calories, with the remaining 50% coming from carbohydrate. Maintaining dietary changes for long periods is very difficult for many persons. Specific self-management skills may ease the task.

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In personal health maintenance, diet can provide a form of prevention or treatment of disease. Some of the most common medical problems treated with diet are those associated with cardiovascular disease. About 80% of persons who are affected by cardiovascular disease have one or more of the primary risk factors: hypercholesterolemia, hypertension or cigarette smoking. Probably next in order after the primary risk factors is diabetes mellitus. Although obesity may not be an independent risk factor, it significantly affects lipid levels, blood pressure and blood glucose level. In this article we will discuss ways hyperlipidemia, hypertension, diabetes mellitus and obesity may be favorably affected by a low-fat, low-cholesterol diet.[1,2]

Diet-Related Factors

Hyperlipidemia

Diet is the cornerstone of treatment for hyperlipidemia. Factors in the diet that affect serum concentrations of lipids and lipoproteins include total calories, consumption of simple carbohydrates and alcohol, intake of cholesterol, the ratio of polyunsaturated fat to saturated fat and the percent of calories derived from carbohydrate, fat and protein.

Results from the recently completed Coronary Primary Prevention Trial[3,4] indicated that by lowering the low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels, the incidence of coronary heart disease morbidity and mortality was diminished.

Table 1 shows the upper limits of normal for cholesterol, triglyceride and high-density lipoprotein levels.[5] There is evidence that elevated cholesterol and LDL-C levels are important risk factors for the development of coronary heart disease, with a strong inverse correlation between high-density lipoprotein levels and the risk of coronary heart disease. The evidence supporting elevated triglyceride levels as a risk for coronary heart disease is not as strong. However, hypertriglyceridemia is a risk factor in persons who have diabetes mellitus or chronic renal disease. An elevation of the triglyceride level may be the result of excessive alcohol use, uncontrolled diabetes or estrogen therapy. In many persons weight reduction and limited alcohol intake lower the triglyceride level. For a person with hypertriglyceridemia who is at a normal weight, a restriction in simple carbohydrate may be necessary. For an overweight person, simple carbohydrate is restricted as part of the weight-reducing diet. Reducing the blood triglyceride level usually inversely affects the high-density lipoprotein level. Exercise is a beneficial adjunct for decreasing triglycerides.

Hypercholesterolemia is affected by both the amount and kind of dietary fat. Saturated fat tends to raise the cholesterol and LDL-C concentrations, polyunsaturated fat tends to lower them and monounsaturated fat has little or no effect. Weight reduction may also help lower cholesterol levels.

Hypertension

Hypertension, one of the major risk factors of coronary heart disease, affects about one out of every four persons between the ages of 18 and 79 years. Elevated blood pressure is usually defined as 140/90 mm of mercury or greater. The risk for coronary heart disease gets progressively greater as the pressure increases. The primary dietary goals for treating hypertension are to control sodium intake and maintain an ideal body weight.

All foods contain sodium in varying amounts. Processed foods have a much higher content than unprocessed foods. About half of the average sodium intake is from salt or sodium compounds added during processing. The remainder is divided between salt added during home preparation and that occurring naturally.

Sodium restrictions can vary from as low as 200 to 500 mg to as high as 3,500 mg or "no added salt." The most common restriction is 2,000 mg of sodium per day, which is effective

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TABLE 1.—*Hyperlipidemia Values**

Age, Years	90th Percentile Cholesterol, mg/dl ♂	90th Percentile Cholesterol, mg/dl ♀	90th Percentile Triglyceride, mg/dl ♂	90th Percentile Triglyceride, mg/dl ♀	10th Percentile HDL, mg/dl ♂	10th Percentile HDL, mg/dl ♀
0-19	185	190	120	120	35	40
20-24	205	215	165	145	30	35
25-29	225	220	200	145	30	40
30-34	240	220	215	145	30	40
35-44	250	230	250	160	30	40
45-54	260	255	250	185	30	40
55-64	260	275	235	200	30	40
65+	260	275	210	205	35	40

HDL=high-density lipoprotein

*Adapted from Rifkind and Segal.[5]

for most persons. This can be accomplished by counting milligrams of sodium or avoiding high-sodium foods.

Diabetes Mellitus

Diabetes mellitus is defined as a deficiency of insulin and is characterized by an increase in the concentration of plasma glucose. Diabetes is classified as either type I, insulin-dependent, or type II, noninsulin-dependent. The factors for treating diabetes include diet, insulin (for type I) and exercise. Death from diabetes is due to complications over a long period of time. Diet plays a significant role in controlling blood glucose for insulin-dependent and noninsulin-dependent diabetes. About 80% of persons with type II diabetes are overweight. A low-cholesterol eating plan, such as The Living Heart Diet,[1] can be used for treating such persons because it controls carbohydrate and fat.

Obesity

Obesity is frequently defined as 20% or more above ideal body weight. A person's ideal weight can be determined by (1) using a height-weight table; (2) allowing 100 lb (45 kg) for the first 5 ft (1½ m) for women and 106 lb (48 kg) for men, plus 5 lb (2¼ kg) for each additional inch (2½ cm) for women and 6 lb (2¾ kg) for men, or (3) using a body volume test.

An estimated 80 million Americans are overweight. Weight reduction can be achieved by reducing intake of calories and increasing the amount of exercise. Behavioral strategies, described later in this article, are beneficial for maintaining dietary changes.

The Living Heart Diet

The Living Heart Diet recommends that 30% to 35% of total calories come from fat, with up to 10% polyunsaturated fat, less than 10% saturated fat and the remainder monounsaturated fat. Protein and carbohydrate make up 20% and 50%, respectively, of calories. Dietary cholesterol is limited to 300 mg daily. The Living Heart Diet is designed to lower both cholesterol and triglyceride to safe, acceptable levels. If this is not accomplished, the cholesterol and fat can be decreased to 200 mg and 30%, respectively. The diet can be still more restricted if additional lipid lowering is desirable. Fat can be decreased to 20% of calories and cholesterol to 100 mg per day. This process of gradually restricting the diet is called a "phased approach." It is similar to the diet program recommended by the American Heart Association for treatment of hyperlipidemia.[6] The phased approach is based on the idea that a person should not be asked to follow a diet any more restricted than necessary. If lipids reach an acceptable level with only a moderate restriction of fat and cholesterol, that is the level at which a person should be maintained, not a more restricted one.

Each level of The Living Heart Diet can be modified to achieve a desirable caloric and sodium level. Several techniques can be used to help persons accomplish their dietary goals.

- *Counting* can be used to add up the number of calories, milligrams of sodium or grams of fat on food records (described below). It can be used to monitor any dietary component that needs to be limited. This technique allows flexibility in selecting preferred foods that may otherwise not be "allowed." For example, persons on a 2,000-mg sodium diet can have cured ham, pretzels or other "high-sodium" foods if they are keeping track of their total sodium intake and staying within the recommended range.
- *Exchanging* can also be used along with food records. In an exchange system, foods are divided into groups such as breads, fruits, dairy products and meats. One exchange is usually one serving of a food. A specified number of exchanges is allowed from each group. The number varies according to the desired caloric level.
- *Restricting* foods high in a certain dietary component is another technique for controlling the diet. Persons are given lists of foods that are "high" and "low" in sodium, saturated fat or cholesterol. They are told to select from the "low" or "allowed" lists and not to eat foods on the "high" or "avoid" lists.

Food Groups for The Living Heart Diet

Meat, Poultry and Seafood

This food group provides protein needed for growth, maintenance and repair of tissues and cells. Protein requirements vary according to age and sex. Adults need about 0.8 grams of protein per kg of body weight and children and teenagers, 1.8 and 1.0 grams, respectively. For an 80-kg (176-lb) adult, the protein requirement is 64 grams a day. The National Food Consumption Survey showed that the average American man consumes 10 oz of meat a day, which yields about 80 grams of protein, or a third more than necessary. Other food groups also provide good sources of protein—dairy products and the bread, cereal and starchy foods group.

The meat group provides more fat in the typical American diet (about 41%) than any other single food group.[7] Often it is not just fat in the meat itself, but fat (such as shortening or butter) added during cooking, or as a sauce or gravy. Fat content varies according to the kind of meat, from less than 2% in many types of fish to as much as 45% in luncheon meat and sausage (Table 2).

Seafood, including shellfish and finfish, provides less fat per gram of protein than poultry, beef or pork. It is the preferred choice on The Living Heart Diet. Seafood contains several polyunsaturated fatty acids not found in significant amounts in other foods, especially docosahexaenoic acid and eicosapentaenoic acid. Increased levels of these fatty acids help decrease serum cholesterol.

Poultry is also low in saturated fat. Removing the skin of chicken before cooking reduces the fat even more because the fat stored beneath the skin penetrates lean tissue during the

cooking process. This is not true for turkey; therefore, the skin does not need to be removed before cooking.

Beef ranges from 8% to 45% fat after the fat has been trimmed. Veal and calf, younger forms of beef, are lower in fat than older animals. Lean, trimmed veal has about 2% fat. Beef, pork and lamb with no more than 10% fat are allowed on The Living Heart Diet. Organ meats, such as brain, heart, liver and kidney, are concentrated sources of cholesterol and are allowed in very limited amounts, if at all. Amounts of meat are specified in Table 3.

Egg

Egg yolk is the most concentrated source of cholesterol—274 mg for a large egg. On The Living Heart Diet, which allows 300 mg of cholesterol a day, eggs are limited to two yolks per week.

Fat

The amount and kind of fat in the diet affect the serum cholesterol level. The first phase of The Living Heart Diet recommends 30% to 35% fat. The average American diet has about 43% fat.[11] Fat is the most concentrated source of calories: It has more than twice as many calories per unit as protein or carbohydrate—9, 4 and 4 calories per gram, respectively. Alcohol has 7 calories per gram. The three types of fatty acids—saturated, polyunsaturated and monounsaturated—have comparable caloric values.

Saturated fats occur naturally in all animal products and in a few vegetable products. Examples of these include fat on meat and in dairy products (cream, cheese, whole milk and butter). Vegetable sources of saturated fat include palm, palm kernel, coconut oil and cocoa butter. These vegetable oils are used in commercial products because of their long shelf-life. Products containing these vegetable saturated fats include nondairy creamers and whipped toppings, crackers, bakery products and all varieties of chocolate. Cocoa powder is a form of chocolate that is not saturated as most of the fat has been removed.

Polyunsaturated fats, listed in descending order of polyunsaturation, include safflower, corn, sunflower, soybean and cottonseed oils. The fat in fish is also polyunsaturated. Some studies have suggested that long-term consumption of large amounts of polyunsaturated fat may present a potential risk of cancer developing; this has not been substantiated, however. A high ratio of polyunsaturated to saturated fat is only recommended for treatment of severe hypercholesterolemia, not for the general public. Monounsaturated fats include olives, olive oil, peanuts, peanut oil, peanut butter and avocado. Amounts of fat-containing foods that make up a serving are listed in Table 3.

Dairy Products

Dairy products provide a rich source of calcium in the form of cheese, milk and yogurt. These foods can also be high in saturated fat; however, there are low-fat varieties of each (Table 3). Low-fat cheese (yellow and white), low-fat or skim

TABLE 2.—*Percent Fat in Meat, Poultry and Seafood*

	Percent Fat
Seafood*	
Clams, raw	2.5
Flounder, raw	0.8
Haddock, raw	0.1
Salmon, pink (humpback), raw	3.7
Snapper, red and gray, raw	0.9
Shrimp, raw	0.8
Tuna, water packed	0.8
Tuna, oil packed	8.2
Poultry†	
Chicken, light meat, no skin, roasted	4.5
Chicken, dark meat, no skin, roasted	9.7
Chicken, light and dark meat, with skin, roasted	13.6
Turkey, light meat, no skin, roasted	3.2
Turkey, dark meat, no skin, roasted	7.2
Turkey, light and dark meat, with skin, roasted	9.7
Beef*	
Flank, round (lean only), cooked	6.1
Chuck, porterhouse, T-bone (lean only), cooked	10.3
Ground beef, regular, cooked	20.3
Lamb*	
Shoulder (lean only), cooked	9.6
Pork*	
Ham (lean only), cooked	9.0
Spareribs (lean and fat), cooked	35.1
Luncheon Meat and Sausage‡	
Bologna, beef	28.4
Italian sausage, cooked, pork	25.7
Pepperoni, pork and beef	43.9
Salami, dry, pork	33.7
Summer sausage, beef and pork	29.9

*Modified from Watt and Merrill.[8]
†Modified from Posati.[9]
‡Modified from Richardson et al.[10]

milk and low-fat or nonfat yogurt have comparable amounts of calcium to their high-fat counterparts.

Bread, Cereal and Starchy Foods

This food group provides protein, vitamins, minerals, fiber and energy. It includes bread and cereal products, pastas, crackers, starchy vegetables and dessert items made with "allowed" ingredients (polyunsaturated fat, low-fat or skim dairy products and egg substitute or egg white). Alcohol is also categorized in this group as a means of accounting for its calories. No more than two servings of alcoholic beverages are recommended per day because of its tendency to increase weight and triglyceride levels. A list of foods in this group is in Table 3.

The bread, cereal and starchy foods group is a good source of fiber. Fiber is material in the diet that is resistant to digestion, provides bulk, holds water and exchange ions and binds small organic molecules. It has been suggested that fiber may play a role in reducing the risk of cardiovascular disease.

Fruit and Nonstarchy Vegetables

Fruit is a source of simple carbohydrate, vegetables of complex carbohydrate. Both provide good sources of vitamins and minerals, expecially vitamins A and C.

Eating Away From Home

It is estimated that at least one out of every three meals is eaten away from home. It is possible to follow The Living Heart Diet in most restaurants, but selecting a restaurant is a key factor. Restaurants that offer a wide variety of foods are more likely to have low-fat selections than places that have only one type of food, such as pizza, hot dogs or fried chicken. Making the decision ahead of time to select healthful low-fat foods is important. In a restaurant, ask the table server how food is prepared and request assistance with ordering. Guidelines for selecting from a menu include the following:

Beverages

Coffee, tea, club soda, bottled waters and sugar-free carbonated drinks (if calories need to be limited) are available in most restaurants. If caffeine needs to be avoided, decaffeinated beverages can be requested or one's own tea or coffee can be provided and a pot of hot water requested.

Alcohol adds calories; however, if a mixed drink is ordered, the "mixer" can be low in calories. For example, sugar-free carbonated beverages, water and juices are lower in calories than presweetened mixes. A spritzer (wine with seltzer) contains fewer calories than wine by itself. Some drinks such as a bloody mary can be ordered without the alcohol (tomato juice is high in sodium).

Appetizers and Salads

Fresh fruit or vegetables, steamed seafood or vegetable soup are low-fat appetizers. Salads can be ordered without dressing or the dressing can be served "on the side." Small amounts of French, thousand island or Italian dressing can be used because they are made with soybean or cottonseed oil, or both. Lemon and vinegar are good salad enhancers. Some low-fat choices in ethnic restaurants include

French—steamed mussels;

Greek—tzatziki;

TABLE 3.—*The Living Heart Diet Food Groups and Serving Sizes*

Meat, Seafood, Poultry (60 kcal/oz)
1 oz lean meat, poultry, seafood
1/4 cup cooked or flaked meat
Dairy Products (80 kcal/serving)
1 cup skim or low-fat milk
1/3 cup low-fat cottage cheese
2 oz low-fat cheese (1% to 5% butterfat)
1 cup plain low-fat or nonfat yogurt
Bread, Cereal and Starchy Foods (70 kcal/serving)
1 slice bread
1/2 cup cooked cereal, pasta, rice, grits
3/4 cup flake-type cereal
1/3 cup frozen yogurt*, ice milk*
1/4 cup sherbet*
3 cups popcorn (air popped)
1-1/2 oz whiskey†
4 oz table wine†
12 oz beer†
Fats (45 kcal/serving)
1 tsp oil or margarine
2 tsp salad dressing or peanut butter
5 to 6 pecan or walnut halves
10 peanuts
1 tbsp sunflower seeds or avocado
10 small olives
Fruit (40 kcal/serving)
1/2 cup unsweetened fruit or juice
Nonstarchy Vegetables (25 kcal/serving)
1/2 cup cooked or 1 cup raw nonstarchy vegetables

*These foods have a high sugar content and should not be used frequently.
†Limit to 2 servings of alcohol per day.

Indian—raita;
Middle Eastern—midya dolma, yalanji, yaprak, imam bayildi.

Entrees

Seafood is usually the best selection in a restaurant because it is naturally low in fat. Seafood, like all other types of meat, should be broiled, boiled, steamed, poached, roasted or baked without fat. Often broiled and baked meats are basted with fat, and "broil dry" should be specified when ordering. Sauces and gravies can be served as a side dish. The following are some low-fat entrees in ethnic restaurants:
Chinese—food broiled, steamed or lightly stir-fried in vegetable oil, served with rice;
Greek—plaki or shish kebob served with rice;
Indian—tandoori chicken, fish marinated in spices and seekh kebob;
Italian—marsala or marinara sauce on pasta or lean meat;
Japanese—sashimi, sushi, nabemono or chicken teriyaki;
Mexican—fajitas, tacos al carbon served with soft corn tortilla, or seviche;
Middle Eastern—shish kebob, or manter kebob;
Steakhouse—London broil, flank steak or kebob.

Vegetables and Side Dishes

Most cooked vegetables are seasoned with fat (often butter). To get "plain" vegetables, it may be necessary for the person to specify that to the waiter. Lemon brings out the flavor in many vegetables—even a baked potato. Sauces can be served on the side. A few suggestions in ethnic restaurants follow:
French—wine sauce, such as bordelaise, is usually low in fat;
Indian—lentils or dals;
Mexican—guacamole (small serving because it is high in fat).

Dessert

Fresh fruit is the best selection. Often melon or berries are available even if they do not appear on the menu. Other low-fat choices include sherbet, fruit ice, frozen yogurt, gelatin and angelfood cake.

Staying on The Living Heart Diet

Dietary habits learned early in life are difficult to change. By the time we turn 40, we have already eaten more than 40,000 meals plus an untold number of snacks. It is no wonder people have problems making changes; eating patterns reinforced with such frequency will not yield without great struggle. By the time we become adults, our preferences for certain foods are so well established that to make even minor shifts for long periods often requires Herculean effort.

We have found that changing both the kinds of food people eat and their specific eating behaviors requires training in the development of self-management skills. All of us can make temporary changes in our eating pattern. We go on a brief diet to lose a few pounds or cut down on the amount of coffee we are drinking, the amount of salt we are using or the number of eggs we are eating. To make these changes permanent, however, requires much more work than calling on our willpower, a transient phenomenon at best. To make changes in our diet last a lifetime requires a major commitment. Although there is as yet no easy magic formula that works for everyone, we have found that several behavioral strategies do seem to help people make the difficult task of adhering to changes in diet somewhat less arduous. The strategies are applicable to achieve any desired dietary change.

Self-Monitoring

After determining what changes are needed, usually by working closely with a dietitian, the first step in changing a diet is self-monitoring. Everything eaten or drunk, including quantity and calories, should be recorded in a notebook, along with the behaviors associated with eating (time, place and circumstances). The act of writing everything down increases the awareness of eating and helps a person learn caloric values of food. Self-monitoring is not easy and can be boring, monotonous, time-consuming and complicated. If done conscientiously, however, the recording can have a positive effect on dietary change.

Problem Solving

A problem-solving strategy is helpful in maintaining dietary changes because difficulties in living occur frequently and need to be dealt with quickly. We have found the "personal science"[12] approach helpful. Using the mnemonic "science," seven specific skills for successfully resolving daily dietary problems are as follows:

- Specify the problem;
- Collect information on it;
- Identify specific causes or patterns;
- Examine options;
- Narrow the options and try some out;
- Compare the data, and
- Extend, revise or replace the data.

The problems of staying on an eating plan are amenable to scientific solutions, and the specific skills taught are similar to scientific research skills. Persons should be able to use this model to help them deal with any dietary problems that develop. This approach is particularly useful with well-educated people and is less helpful with poorly educated persons. With them, we use more simple self-monitoring strategies with specific assignments and short-term contracts.

Cognitive Strategies

Thoughts and attitudes often play a major role in maintaining poor dietary behavior. A "thoughts diary" is sometimes helpful in uncovering beliefs about food. Writing down food-related thoughts at random times during a week may elicit negative patterns. Repeating counterstatements several times a day can weaken pessimistic thoughts. For example, a person who says, "I'll never be able to stay on The Living Heart Diet; I've never stayed on one for more than a week," may repeat a counterstatement like "I know some excellent new strategies to help me stay on my eating plan this time. There is a first time for everything and I'm going to do it." The following steps can help change negative thought patterns to positive ones:

- Write down food-related thoughts.
- Evaluate whether they are discouraging, unreasonable or self-defeating.

- Actively change them by substituting encouraging, positive self-comments.

Another cognitive strategy that is helpful for some people is visual imagery. Persons are taught to relax, then visualize themselves in upcoming difficult food-related situations. For example, if they know that they will be attending a buffet party over the weekend, they imagine themselves there, having a wonderful time and staying on their eating plan. It is important for them to actually imagine themselves at the party, picking and choosing appropriate foods. This imaginal rehearsal will give them practice and help them to use self-control at the party.[13]

Urge Control

Some people experience almost uncontrollable urges to eat inappropriate foods. A craving for sweets sometimes leads to a cookie or candy binge. Learning to control urges helps persons to stay on their eating plan. Several strategies may be used. We teach people to engage in another behavior whenever an urge occurs. For example, telephoning a friend or talking with a family member for about 10 minutes is often enough time for the urge to pass. Another technique is for persons to first ask themselves whether they really want to eat the food more than they want to stay on their eating plan. If they decide to eat the food, they should do it in front of a mirror and write down everything they eat on a self-monitoring form. A third strategy involves having them fill out a form that asks specific questions about the urge each time it occurs—that is, how strong it is, what made it occur and the like.[13]

Stimulus Control

Self-monitoring diaries will show a number of patterns of inappropriate eating. Stimulus control strategies can often be useful in modifying these patterns. Examples of typical stimulus control techniques involve hanging helpful reminder signs and pictures on the refrigerator door and throughout the home, limiting all at-home eating to the dining room table and paying more attention to food at mealtimes by turning off the television set or radio.[13]

Contingency Contracting

Explicit reward systems can help increase motivation to stay on an eating plan. Points can be awarded for completing behavioral assignments, like weighing themselves each day or writing down all they eat or making specific changes in their diet. After earning some specified number of points, they reward themselves with some predetermined treat, like going to a concert or buying a new record or tape. These contracts work best if they are written and administered by a second person.[13]

Stress Management

Some people lose control over their eating during periods of stress or anxiety. Relaxation training may help during these periods. All relaxation strategies take practice but most persons can learn the skill in about a month if they practice regularly. Progressive relaxation, which requires tensing and relaxing muscles, is a widely used procedure and can be learned fairly easily in about a month by practicing twice a day for 15 minutes a session. When mastered, the procedure can be used when persons notice themselves thinking about food at inappropriate times. One example would be while viewing television; when an attractive food is displayed, the relaxation technique can be used to lessen psychological cravings.[13]

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Smoking and Health

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Although cigarette smoking is the number one public health problem in the United States, physicians have failed to take the lead either in convincing youngsters not to begin smoking or in aiding adults to quit smoking. To be most effective and convincing in combating the smoking epidemic, practicing physicians must have the same basic fund of knowledge about the short- and long-term consequences of smoking as they do about other commonly encountered medical problems. By acting on such knowledge and adopting a definite set of attitudes and activities in their offices and with patients, physicians can make a significant contribution to their patients and to the entire community in which they practice.

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Cigarette smoking is the number one public health problem in the United States. It is related to more than 350,000 premature deaths each year: 170,000 from coronary heart disease, 130,000 from cancer and 50,000 from chronic obstructive lung disease.[1] This does not include fetal and neonatal deaths caused by smoking by pregnant women, nor does it include the more than 2,300 deaths caused by fires attributed to cigarette smoking (1981 National Fire Incidence Reporting System and Federal Emergency Management Agency [FEMA] analysis of National Fire Protection Association survey data, available from FEMA, US Fire Administration).

Role of Physicians

The role of physicians in the prevention, diagnosis and treatment of tobacco-related diseases has largely been restricted to diagnosis and treatment. While specialists in various categories abound and multiply, there is no specialty that deals with preventing youngsters or adults from beginning to smoke and there is no specialty that deals with the problems of smoking cessation. Our other great social aberrations—alcohol and drug abuse—are beginning to attract physicians and other health professionals into careers dedicated not only to diagnosis and treatment, but prevention and, especially, cessation activities. There may be any number of reasons, none particularly valid, why physicians do not spend more time in emphasizing the avoidance of smoking in their practices:

- The subject was covered poorly in medical school.
- The subject was covered poorly in residencies.
- The physician smokes.
- Third-party payors and individual patients do not pay for advice or counsel on techniques for breaking the smoking "habit" or nicotine addiction.
- Smoking is so pervasive in our society that until the 1960s it had been the norm, still is frequent and physicians risk losing their patients if they display a zeal in rooting out what some of our smoking citizens feel is a constitutional right.
- There is no significant body of scientific knowledge concerning smoking initiation and cessation upon which practicing physicians can rely when they advise patients not to begin smoking or to quit. The recent recognition that nicotine addiction is a significant aspect of the smoking habit and the availability of nicotine chewing gum are steps in the right direction, according to some authors but not according to others.[2]

Given all these potential negatives, there is much that physicians can do to enhance positive personal health behavior among their patients because 92%[3] of adolescents and 85% of adults who smoke wish to quit.[4]

Why Do Americans Smoke?

Unlike food and oxygen, tobacco is not one of life's necessities. All tobacco use—smoking, chewing and sniffing—is learned behavior, begun as a result of direct and indirect social pressures. For the rest of this discussion the primary focus will be on cigarette smoking.

Physicians dealing with children and adolescents should be aware of the multiple reasons why their young patients experiment with cigarette smoking. Children are most likely to smoke if both parents smoke, less likely if one parent smokes and least likely if neither parent smokes. Children from sin-

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gle-parent homes are more likely to smoke than those from two-parent homes. Children who do poorly academically or in athletics (or both) are more likely to smoke than their more successful peers.[5,6]

The barrage of print advertising and the use of cigarettes by movie stars suggest that a person who smokes cigarettes is popular, attractive, active, sophisticated and definitely adult. The opposite is true. Some youngsters begin to smoke as a result of peer pressure from a group they wish to join or imitate, whereas others smoke to overcome feelings of inferiority. Before becoming addicted to nicotine, a smoker may use cigarettes to reduce tension in social situations, to occupy his or her hands, to relax, to become stimulated or any combination of the above. The point to be made is that there is no single reason for beginning smoking applicable to all persons. Accordingly, techniques to prevent youngsters from beginning smoking or techniques for helping any child, adolescent or adult to quit smoking must be individualized to the maximum extent possible.

Because smoking is a learned behavior, the most successful programs combine favorable home, school, work and recreational environments with positive programs of physical and psychical alternatives to smoking as well as knowledge of both the short-term and long-term health, economic and social adverse consequences of smoking. Many of the determinants currently linked to smoking initiation are beyond the control and purview of physicians. But almost all physicians can play a far more active and far more vital role in the health maintenance of their patients if they become knowledgeable about the untapped potential their professional encounters with patients offer.

A physician's private office presents the first opportunity to inform patients of both the medical consequences and the social undesirability of smoking. Literature on the health hazards of smoking, generally, and of the health hazards pertinent to that physician's specialty should be available. There should be literature available on how to quit smoking and information on organized smoking-cessation groups and other self-help aids. A physician's office should display "no smoking" signs and there should be no ashtrays available for those who wish to disregard the signs. Magazines for the waiting areas should be selected from among those publications that do not accept cigarette advertisements.

Physicians themselves should be nonsmoking role models and should demand the same of all of their employees. They should take a complete smoking history and use the opportunity of both the history and physical examination to educate patients about the health hazards of smoking and the healthful consequences of quitting if a patient smokes.

It is important for physicians to realize that more than 95% of the 33 million ex-smokers in the United States have quit without formal, organized and costly proprietary "quitting" programs. A physician's counsel to quit following a frank discussion of the consequences of not quitting may be sufficient motivation in millions of instances for a person to quit. Recent national polls show that a fourth to half of then-current smokers did not know that smoking causes almost 90% of lung cancers, one third to two thirds of those queried did not know that smoking causes heart attacks and emphysema, half of women queried in 1980 did not know that smoking during pregnancy increases the risk of fetal mortality and a third of those queried in 1978 did not know that smoking by a 30-year-old person reduces life expectancy.[7]

While each physician need not be a professional analyst, all physicians should be able to offer encouragement and advice to a patient who smokes, such as

- Make the firm psychologic decision to quit.
- Associate with nonsmokers and former smokers.
- Enlist family and friends to encourage nonsmoking.
- Avoid situations in which smoking would be encouraged.
- Avoid other situations that a patient specifically identifies with smoking.
- Most important, substitute healthful behavior, such as an exercise program, proper eating and drinking habits, appropriate recreation and chewing gum, including nicotine-containing gum.
- Ask others not to smoke in the patient's presence.
- Get rid of all smoking adjuncts—cigarettes, ashtrays and the like.
- Make a public commitment to family, friends and coworkers to quit smoking.
- Join a group opposed to smoking for positive reinforcement.

These ten suggestions have worked for millions of Americans and will work for millions more if emphasized by their personal physicians.

Physicians and their staffs should offer psychologic counsel and advice to those who wish to quit. Support and encouragement in person and by phone from health professionals during the first days and weeks of a smoker's withdrawal from cigarette smoking (nicotine) may mean the difference between success and failure.

In the hospitals they use, physicians should encourage, insist and persist with hospital administrators to ban smoking in patient rooms, public areas, waiting areas, cafeterias and meeting rooms. They should encourage hospital administrators to promote "Quit Smoking Clinics" and health education programs as a community service.

Physicians should be active in helping promote nonsmoking activities in voluntary health groups—the American Cancer Society, the American Lung Association and the American Heart Association—and their local, state and national medical organizations.

Physicians should be available as expert lecturers or speakers at schools and before groups of employees interested in health maintenance or health promotion. They should use the public media to speak out on the harmful health consequences of smoking and support legislative measures to restrict smoking in public places.

The United States is suffering from an epidemic of smoking-related diseases. A physician's role in combating smoking cannot be restricted to the time spent in the examining room alone. Smoking is a complex behavior, leading to disability or death from a variety of diseases. If all physicians reacted to this epidemic as they should and would to the deliberate introduction of a new disease vector that would kill 350,000 Americans each year, our patient population surely would get the message. Our own laxity, lassitude, acceptance and sometimes encouragement of the cigarette industry's advertising, distribution and sale of the billions of deadly, rolled tubes of tobacco confuse our patients and somehow reassure

them—as the industry advertising cleverly attempts to do—that there is no relationship between smoking and disease, that nothing is proved and that there is an honest debate among equally competent medical scientists whether or not cigarette smoking is harmful. But if all 400,000 physicians were to become active, the national impact would be enormous and many millions of smokers would quit; as more and more smokers quit, the smoking habit would become less socially acceptable and even more millions would quit.

On a personal note, I can remember 20 years ago suggesting that the American Association for Cancer Research and the American Cancer Society adopt a no-smoking policy—to no avail at that time. I can remember 16 years ago suggesting that the National Cancer Institute staff adopt a no-smoking policy—to no avail. I can remember 13 years ago suggesting—nay, ordering—in the Federal Register, that the United States Public Health Service adopt a no-smoking policy; that was successful because I was then the Surgeon General. But just two years later as a department chair at the Mayo Clinic I suggested a no-smoking policy at staff meetings—again, to no avail. I will not recount any other failures or successes, except to say that each of our individual actions does make a difference. All of the above groups and many more have by 1984 adopted no-smoking policies.

While the amount of scientific research on the role of cigarette smoking in the etiology and pathophysiology of cancer, cardiovascular, pulmonary and fetal-maternal disorders is voluminous, with more than 30,000 published scientific studies, relatively scant research has been carried out on the psychological and physiologic reasons for either smoking initiation or smoking cessation. Recent Surgeon Generals' reports provide more data on the latter subjects and on passive or involuntary smoking, but the research effort is miniscule compared with the magnitude of the problem.

For physicians to be effective in promoting health among their patients, they should be familiar with the current successful techniques for healthful behavioral modification, generally accepted by social scientists concerned with positively modifying Americans' life-style.

Programs emphasizing long-term adverse health consequences of smoking have less effect on dissuading youngsters and adolescents from beginning smoking than more positive approaches emphasizing the benefits of healthful habits such as exercising, eating wholesome foods and having positive social interactions with peer groups that are engaged in healthy life-styles. The short-term consequences of smoking such as early impairment of lung function as shown by special pulmonary function tests, smokers' breath, the expense of the cigarette habit and the social undesirability or unacceptability of smoking also have a place in an overall program of positive health maintenance or enhancement. Lectures by teachers are less effective than information provided by peers or student leaders who are given special instruction in health-promoting behavior and then given the opportunity to interact and answer questions from their classmates.

Specially prepared instructional material for school use is being tested in a number of school systems, including questionnaires, interactive computer programs, peer lectures as described, health educators' lectures and discussions and physician and other health professionals giving lectures and participating in school discussions.

Because many youngsters will have been smoking regularly before they are exposed to such programs, persons responsible for health education should be familiar with the various smoking-cessation techniques and methods. They should realize that the shorter the time a person smokes, the more likely that person is to quit; the fewer cigarettes smoked each day, the more likely he or she will be able to successfully give them up; the more times a person tries to quit, the more likely that person will achieve permanent success and become a former smoker.[8] This general information applies to both men and women and from youth through middle age.

It is important for physicians, particularly, to know the data on the multiple health hazards associated with smoking because national polls continue to show that many smokers do not associate smoking with cardiovascular disease, pulmonary disease, maternal and fetal disease and death and even cancers, perhaps as a result of "denial" by those already addicted to nicotine and perhaps as a result of persuasive cigarette advertising associating cigarette smoking with healthy, handsome, athletic young adults engaged in pleasurable pursuits.

The following brief summary of the medical data should be part of the mental armamentarium of all physicians and used as appropriate in their health maintenance and promotion activities.

Diseases Associated With Smoking

Cancer

Cigarette smoking is a major cause of cancer of the lung, larynx, esophagus and oral cavity and a contributory factor in causing cancer of the urinary bladder, kidney and pancreas in both men and women. For male smokers cancer death rates are twice those of nonsmokers. For female smokers cancer death rates are 30% greater than for nonsmokers and are increasing. There is a dose-response relationship in both men and women between the number of cigarettes smoked per day and the likelihood of dying from cancer. Beginning several years after stopping smoking, the mortality rate from cancer declines for a former smoker towards the rates of a nonsmoker. After 15 years as a nonsmoker, however, a person who had many years' exposure as a heavy smoker is still twice as likely as a lifetime nonsmoker to have lung cancer develop.[5]

Lung Cancer

The epidemic of lung cancer shows no sign of abating. Since the early 1950s it has been the most common cause of death from cancer in American men. Lung cancer will be the most common cause of death from cancer in women in the US by 1986. The rate of increase of age-adjusted lung cancer incidence and deaths is rising in women while the rate of increase is falling in men, though the number of deaths expected from lung cancer in men (85,000) far exceeds that expected among women (36,000) in 1984.[9]

In the United States cigarette smoking is the major cause of lung cancer in men (about 85% of cases). Lung cancer mortality increases with the number of cigarettes smoked, the level of tar and nicotine, the absence of filters, the depth of inhalation, the number of years a person smokes and the presence of other factors such as exposure to asbestos, certain types of mining and other less well-proved occupational exposures.[5] In addition, lung cancer mortality varies inversely

with the length of the cigarette butt and the age a person begins smoking.

A decade ago the Public Health Service advised smokers who were unable to quit smoking to smoke in a less hazardous way—that is, filtered cigarettes, lower tar and nicotine cigarettes, fewer cigarettes per day, less or no inhalation and fewer puffs per cigarette. To a minor extent this has helped reduce the rate of increase of the lung cancer epidemic in men, but the best way to prevent lung cancer is not to smoke at all. There is no firm evidence that smoking filter-tipped, low-tar, low-nicotine cigarettes protects against the development of cardiovascular or pulmonary diseases or the adverse effects on fetuses.[6,8]

A man who smokes 2 packs a day has a 15 to 25 times greater likelihood of lung cancer developing than his nonsmoking companion.

Pipe and cigar smokers also are at risk of lung cancer developing, but because among other factors the alkalinity of pipe and cigar smoke is so high, most smokers refrain from inhaling. The risk of lung cancer among pipe and cigar smokers is therefore much less than that for a cigarette smoker who usually inhales the mildly acidic cigarette smoke. For those pipe and cigar smokers who inhale, however, the risk of lung cancer increases significantly. The risk for cancer of the oral cavity, larynx and esophagus among cigar and pipe smokers is similar to that for cigarette smokers. If the smoke reaches sensitive tissues, the risk of cancer developing is similar. This is consistent with carcinogenicity studies on animals showing that pipe and cigar tobacco smoke condensates are just as carcinogenic as the condensates from cigarette smoke.

Data implicating cigarette smoking as the major causative factor in lung cancer are consistent from many large retrospective and prospective epidemiologic studies, from multiple carcinogenesis studies on animals and from pathologic examination of tissue specimens from humans who never smoked, quit smoking, were moderate or were heavy smokers and from those with lung cancer diagnosed early and those with advanced lung cancer.[5]

Cancer of the Larynx

Cigarette smoking is the major causative factor for laryngeal cancer (1% of cancer deaths). The quantitative strength of the relationship between laryngeal cancer and smoking is similar to that for lung cancer. Heavy smokers have a 20 to 30 times greater likelihood that laryngeal cancer will develop than do nonsmokers. Laryngeal cancer is as likely to develop in cigar and pipe smokers as in cigarette smokers with equivalent tobacco smoke exposure. Alcohol use (or abuse) acts synergistically with tobacco smoke to increase the likelihood for the development of laryngeal cancer.[5]

Oral Cancer

Oral cancers include those of the lip, tongue, salivary glands, oral cavity and middle and lower pharynx (excluding both larynx and esophagus). Age-adjusted mortality rates in these groups have remained relatively stable except for nonwhite men, who have shown a significant increase in both incidence and mortality.

As with laryngeal cancer, alcohol abuse acts synergistically with tobacco smoke to increase the rate of cancer development. Similarly, these neoplasms are as likely to develop in pipe and cigar smokers as in cigarette smokers. Snuff also is an etiologic factor for cancer of the oral cavity, particularly for cancer of the cheek and gum. The same quantitative associations pertain between these cancers and tobacco use as for cigarette smoking and lung cancer.[5]

Esophagus

Esophageal carcinoma has been increasing significantly in the nonwhite population, particularly in black men, over the past quarter century. As is true of oral and laryngeal cancer, pipe and cigar smokers are equally at risk with cigarette smokers for the development of this lethal neoplasm; patients with this tumor have a median survival of less than six months after diagnosis and a five-year survival rate of less than 3%. As with oral and laryngeal cancer, alcohol abuse acts synergistically to increase the likelihood of carcinogenesis. Also, as with all of the cigarette smoke-induced cancers discussed so far, there is the same quantitative relationship between amount smoked per day, years of smoking, type of cigarette and manner of smoking and a reduced likelihood of cancer occurring following cessation of smoking.[5]

Urinary Bladder Cancer

This cancer is three times as likely to occur in smokers as in nonsmokers. Occupational exposure to certain dyes, rubber and leather products, petroleum products and other organic chemicals may act as additive or synergistic factors in urinary bladder carcinogenesis among smokers.

The quantitative relationships epidemiologically are not so strong with urinary bladder cancer as they are with the cancers developing from direct exposure to tobacco smoke in the respiratory and digestive tracts; nonetheless, smoking cigarettes likely contributes to the causation of carcinoma of the urinary bladder in both men and women.[5]

Kidney Cancer

Data for kidney carcinoma are similar to those for urinary bladder carcinoma, with cigarette smoke acting as a contributory factor in kidney cancer in both men and women. Pipe smokers have a risk for kidney cancer similar to that of cigarette smokers whereas the data on cigar smokers only is insufficient to make any statement regarding causality.[5]

Pancreatic Cancer

Age-adjusted mortality rates for pancreatic cancer have been increasing since 1950, particularly in the nonwhite population. The mean survival for pancreatic cancer after diagnosis is less than six months and the three-year survival rate is less than 2%. As with kidney and urinary bladder cancer the epidemiologic data are not as strong quantitatively with cigarette smoking as they are for lung, larynx and oral cancer. The term "contributory" is used, as opposed to "causative factor" in relating smoking to pancreatic cancer. Ongoing and future epidemiologic, experimental and pathologic studies will confirm or disprove the causative role of smoking in pancreatic cancer.[5]

Other Malignant Lesions

Epidemiologic data on stomach cancer as related to cigarette smoking are confined to an association between the two,

which is less than that for the other cancers discussed. More and more, data on smoking and cancer of the uterine cervix implicate tobacco smoke as an associated or causative factor. Further work is necessary on both these tumors.[5]

Cardiovascular Disease

Cigarette smoking, along with hypertension and high serum cholesterol levels, are major independent risk factors for the development of coronary heart disease in both men and women. The quantitative relationship between the age smoking began, number of cigarettes smoked, number of years a person smoked and a decrease in risk with cessation of smoking are similar to some of the quantitative relationships found in human carcinogenesis epidemiologic studies. Smoking interacts synergistically with other risk factors to increase the likelihood of cardiovascular disease.

There is no good evidence that filter-tipped, low-tar, low-nicotine cigarettes protect a smoker from the development of tobacco-related cardiovascular diseases.

Following an acute myocardial infarction, a person who continues smoking has a greater chance of a second heart attack and sudden cardiac death. When a smoker quits, mortality from coronary heart disease declines promptly. Within a day or days of quitting smoking, carboxyhemoglobin levels, catecholamine levels, platelet adhesiveness, rapid heart rate and myocardial irritability return toward normal.

Sudden Cardiac Death

Sudden cardiac death is more common in cigarette smokers than in nonsmokers. In addition to the increased chance of a myocardial infarction, a smoker's greater myocardial ischemia may promote greater electrical instability of the heart, including a tendency to ventricular fibrillation or sudden death.[8]

Peripheral Vascular Disease

Smoking is a major risk factor for peripheral vascular disease, including Buerger's disease. Smoking also contributes independently to the peripheral vascular disease associated with diabetes mellitus. Continued smoking by a patient with peripheral vascular disease is a contraindication to surgical therapy because surgical success rates are low for such patients who continue the smoking habit.[8]

Atherosclerotic Aortic Aneurysm

Two-pack-a-day cigarette smokers have an eight times greater risk of developing and dying from atherosclerotic aortic aneurysms than nonsmokers. Below two packs a day there is a quantitative relationship, but of lesser magnitude than that associated with heavy smoking.

Thus, epidemiologic, experimental and pathologic studies converge and are congruent with the conclusion that cigarette smoking is a major causative factor in the development of many forms of cardiovascular disease in the United States.[8]

Pulmonary Disease

Lung diseases rank second only to coronary artery disease as a cause of Social Security-compensated disability. Cigarette smoking is the major cause of chronic obstructive lung disease (both chronic bronchitis and emphysema) in the United States in both men and women.

By using careful physiologic studies of lung function, it is possible to show changes in function in teenaged smokers, which is in contrast with the long periods required following initiation of smoking for the development of most smoking-caused cancers. Cigarette smoke interferes with normal ciliary clearance, by which foreign products are removed from the lung. When young persons stop smoking, the findings of pulmonary function tests improve rapidly. In older persons with a long history of smoking and definite chronic obstructive lung disease, cessation of smoking does not result in anatomic replacement of destroyed alveoli; with smoking cessation, however, mucus production and bronchial spasm decrease, bronchial ciliary function improves and the rate of decline of pulmonary function decreases. The damage to alveoli, unfortunately, is permanent and irreversible.

Recent investigations on the mechanisms of the production of lung damage focus on α_1-antiprotease deficiency and the disruption of the usual balance between α_1-antiproteases and elastase induced by cigarette smoking.

Smokers miss more workdays and have longer stays in hospital for respiratory illnesses than do nonsmokers.

Women and Smoking With Emphasis on Pregnancy

Data on pregnant women who smoke clearly show that their babies are lighter and smaller than babies born to nonsmoking mothers. This relationship is independent of all other factors that influence birth weight including race, parity, maternal size, socioeconomic status and sex of the child. There is a dose-response relationship between the amount of maternal smoking and the reduction in birth weight. The risks of spontaneous abortion, fetal death and neonatal death all increase with increasing levels of maternal smoking. The more a mother smokes, the greater the weight of the placenta in relation to the fetus. In addition or perhaps as a result, pregnant women who smoke have a significant increase in the frequency of abruptio placentae, placenta previa, early or late bleeding pregnancy, premature and prolonged rupture of membranes and preterm delivery, with a concomitantly high risk of prenatal death in each of the above instances.

About 14% of all preterm deliveries in the US are to mothers who smoke. Smoking mothers have twice as many low-birth-weight babies (<2,500 grams) as do nonsmoking mothers. Data are insufficient *at this time* to relate increased fetal malformations directly to cigarette smoking.

Carbon monoxide, cyanide, nicotine and a host of other chemicals in cigarette smoke are being studied to try to identify the chemical or chemicals responsible for these unfortunate occurrences in the most vulnerable group of all involuntary smokers—unborn babies.

The sudden infant death syndrome is more common among infants of smoking mothers. In addition, children of parents who smoke have an increased incidence of bronchitis and pneumonia and of hospital admission for respiratory problems in the first years of life. Children born to smoking mothers are not only smaller and weigh less but are slower to develop physically and mentally up through the teen years.

Subarachnoid hemorrhage among female smokers is 5.7 times as common as in nonsmokers. Subarachnoid hemorrhage among female oral contraceptive users is 6.5 times as common as among women who do not use oral contraceptives. Women who both use oral contraceptives and smoke

cigarettes have a risk of subarachnoid hemorrhage 22 times greater than that of women who neither smoke nor use oral contraceptives.

Similar statistics relating to smoking, oral contraceptives and myocardial infarction show that both smoking and oral contraceptive use are major independent risk factors for myocardial infarction. Among women who smoke cigarettes and use an oral contraceptive, there is a synergistic effect, with a much increased risk of myocardial infarction. Women who smoke at any age have at least twice the risk of a myocardial infarction developing as a nonsmoker. This is of particular concern in younger women.

The overall mortality rate for a female smoker is 1.25 times that of a nonsmoker. The two-pack-a-day female smoker has a mortality rate 1.63 times that of the nonsmoker.

As with men, women smokers have more days absent from work, more respiratory disease, more episodes of admission to hospital, more severe and prolonged cough following lower respiratory tract disease and more severe respiratory disease overall, including chronic obstructive lung disease (chronic bronchitis and emphysema), compared with nonsmokers.

Peptic ulcer disease also develops twice as often in women who smoke as in nonsmoking women; the same pattern occurs in men.[6]

Involuntary Smoking

Cigarette smoke irritates the eyes, nose and throat of nonsmokers and may lead to considerable discomfort in patients with allergies or asthma.

Patients with chronic heart and lung disease have been studied with conflicting results on further functional impairment under conditions of the usual household and occupational exposure to cigarette smoke. Heavy exposure to cigarette smoke leads to high levels of carboxyhemoglobin in an involuntary smoker, with resultant untoward physiologic effects.

There are conflicting data regarding involuntary smoking and lung cancer, but the weight of the existing human epidemiologic evidence and the preponderance of findings on studies using animals suggest that involuntary smoking may lead to cancer. Considering the large number of nonsmokers involuntarily exposed to cigarette smoke, this potential public health problem is worthy of far more attention by epidemiologists, public health workers and all others concerned with this country's primary public health problem.[1,5]

Conclusion

Physicians as a group have the lowest incidence of cigarette smoking of any profession or occupation. They also have both the opportunity and obligation to their patients and to society to take a far more active role in eliminating our number one public health problem.

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Alcohol and Drug Use— Is There a 'Safe' Amount?

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All human endeavors are associated with quantifiable risks. Knowledge of the risk is essential for personal health maintenance. Nontherapeutic use of psychoactive drugs poses an important danger to individual persons and society. What are the quantitative estimates of these risks? Are they acceptable?

Because the basic mechanism of the toxic effect of alcohol or other drugs is unknown, deciding on acceptable risks is difficult. Based on current information, the recreational abuse of inhalants, hallucinogens, stimulants, narcotics and sedative-hypnotic drugs poses unacceptable individual and societal risks. Groups at special risk should not consume alcohol or any drug unless they are under medical supervision. The threshold for increased morbidity from the regular use of alcohol in adults is in the range of three to five drinks per day; this rises sharply after six drinks per day. The apparent "safe" level of alcohol consumption appears to be one to two drinks per day. Further basic studies are required to refine these risk estimates.

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Alcohol- and drug-related illnesses are major public health problems in modern society. With insufficient dollars for health care it is certain that individual persons and society will more closely examine ways to maintain personal health. Alcohol and other drugs are widely used for their mind-altering effects. The "use" or "abuse" of mind-altering agents evokes strong feelings. Conflicts of personal freedom and public danger pose difficult political and philosophical questions, especially when prolonged low-dose consumption for recreational purposes is considered. Complex variables of dose, genetic factors, prior drug exposure and drug interactions all present difficult scientific questions. Do we focus on the drug, on protecting society or on protecting the person at risk? Can we easily distinguish voluntary from involuntary risks? Much has been learned recently concerning broad guidelines for approaching these problems. Important decisions for personal health maintenance may require changes in public and private policy. Perhaps the best approach is to ask, is there a "safe" level of alcohol and drug consumption? If a dose of alcohol or a drug is consumed at a given time and place, are there "acceptable" risks? If this risk can be quantitated and scientifically studied, we can more rationally approach the problem. As with all such risk assessments, we are required to make important decisions with incomplete information.

Scope of the Problem

Drug and alcohol consumption are often viewed together. It is useful to approach the data on alcohol first, as alcohol forms the background for many other drug issues. The consumption of alcohol has increased by more than 30% in the past 20 years. Currently more than 200,000 Americans die annually from alcohol-related deaths and as many as a third of adult patients in hospitals have problems related to alcohol abuse. About 20% of our total national expenditure for health care is for problems related to alcohol abuse. Two thirds of all incidents of domestic violence involve the use of alcohol and a third of the cases of child abuse are alcohol related. About 50% of traffic fatalities, fire deaths, rapes and suicides are thought to involve alcohol.[1] One out of every two Americans will be in an alcohol-related traffic accident during his or her lifetime and, on an average weekend night, one out of every ten drivers on the road is under the influence of alcohol.[2]

Another way to estimate the scope of the problem with alcohol is to examine the total amount of alcohol consumed by a given group. It is possible to estimate alcohol consumption

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
HBsAg = hepatitis B surface antigen
HDL = high-density lipoprotein

based on sales taxes collected at the federal, state and local levels. Of the tax dollars collected in the year 1982-1983, the California State Department of Alcohol and Drugs reports that more than $1 billion was collected from alcoholic beverages. The total consumption in California per capita is about 40 gal of alcohol per year: 31 gal of beer, 5.9 gal of wine and 2.8 gal of distilled spirits. This consumption is about 25% greater than the national average. Not only do Californians drink more per capita than the national average but a greater proportion of Californians drink. Of Californians, about 78% drink alcoholic beverages during the year, with 22% abstaining. Nationwide, about 67% drink and 33% abstain.

What is the risk of 40 gal of alcoholic beverage consumed per year? Theoretically, it is possible to epidemiologically study the health consequences of this consumption. Unfortunately, consumption is not evenly distributed. Although it is difficult to quantitate, most reasonable estimates are that between 10% and 15% of the population consume about 75% to 80% of the alcoholic beverages. It is evident from even these rough estimates that a relatively small percentage of the population consumes most of the alcohol.

Another way to estimate the problem is to recognize that alcoholic beverages are freely available as an over-the-counter drug in 60,000 outlets in California. Alcohol is relatively inexpensive, as its price increases at only 70% of the Consumer Price Index. Of greatest concern, perhaps, to a health-conscious society is the recognition that alcoholic beverages contribute $50 per person per year in taxes; yet, the health and social costs are well over $300 per person per year. Only 4% of these taxes are returned for medical services, research or teaching.

Considering our country as a whole, survey data suggest that a third of the adult population consists of abstainers or of persons who seldom take a drink. Another third consists of people who have up to three drinks per week.* The remaining third consumes four or more drinks per week.[3] Because there is likely a dose-response relationship between the amount of alcohol consumed and some of the medical consequences, it is estimated that those consuming the most alcohol will have the greatest medical consequences. The consequences of prolonged and heavy alcohol use in the 15% of the population consuming 75% of the alcohol include excess mortality rates from cirrhosis, accidents, infection and cancer.

Although the history of alcohol intake may be subject to error, Klatsky and co-workers studied ten-year mortality data among four groups of more than 2,000 persons matched for age, sex, race and cigarette smoking.[4] This study depended on classification of the outcome by a death certificate. The cohort for the study was administered a Kaiser Foundation Health Plan questionnaire in which persons were asked two questions about alcohol use: "In the past year did you drink any alcohol? If yes, how many drinks did you usually have?" The options were nine or more per day, six to eight per day, three to five per day or two or fewer per day. The authors matched, by computer, persons reporting a use of more than six drinks to each of three controls: a nondrinker, a person consuming two or fewer drinks and a person taking three to five drinks. The authors studied 97% of all those reporting six or more drinks. They assumed some degree of underreporting of drinking habits, especially among those with heavy alcohol use. The threshold for increased mortality was shown to be in the range of a regular use of three to five drinks; the risk rose sharply at six or more drinks per day.

One may question the accuracy of death certificates as the primary source of mortality statistics. It is also possible with a declining autopsy rate that death certificates may seriously underestimate the prevalence of important diseases. Taylor and colleagues[5] studied the standard autopsy for determining the cause of death and found discrepancies in 40% of cases between findings at autopsy and death certificates. Alcohol-related problems were found in only 36% of death certificates; in contrast, alcohol-related pathology was found in 72% of autopsies. Thus, the use of only death certificates seriously underestimates alcohol-related mortality. Despite the limitations, these data do suggest a threshold of increased mortality related to alcohol in the range of three to five drinks per day.

Immediate Effects

Studying the immediate effects of alcohol on the nervous system provides a reasonable estimate of the risks of alcohol consumption. The response of a person not tolerant to alcohol correlates well with the dose of alcohol administered and the blood alcohol concentration. The neurologic impairments vary with the rate of rise of the alcohol level, prior alcohol exposure, genetic factors, concurrent use of other drugs and absolute dose of alcohol ingested.[6] In a nontolerant person impairment of motor coordination, sensory perception and cognitive function usually occurs at a blood concentration of between 31 and 65 mg per dl.[6] Because alcohol distributes in body water, the resulting concentration will be proportional to body size. Smaller persons will have higher blood concentrations of alcohol than larger persons given the same dose.

Tolerance to alcohol likely occurs at the cellular level. It has been shown that membranes from alcohol-dependent animals resist the acute fluidizing effects of alcohol. It is possible that tolerance may represent cellular adaptation that limits the entry of alcohol into membranes and compensates for the biophysical effects of alcohol within the membranes.[6] Understanding the molecular mechanisms underlying acute intoxication, tolerance and withdrawal may allow for more accurate dose-effects studies.

There are many neurologic diseases associated with the prolonged use of alcohol. Whether the structural neurologic changes associated with this use of alcohol are a result of alcohol toxicity itself or of nutritional deficiencies is unknown. Polyneuropathy, cerebellar degeneration and Wernicke's encephalopathy are common disorders associated with alcohol use. Recent epidemiologic studies have even implicated acute intoxication as a risk factor for ischemic cerebral infarction in young persons.[6] The equivalent of five to six drinks per day is suggested as being related to an increased risk for ischemic cerebral infarction in persons younger than 40 years. It is possible that these changes are

*One drink is estimated to be about 30 ml (1 oz) of 86-proof alcohol containing approximately 10 grams of alcohol.

related to osmolality, changes in coagulation or altered blood pressure. A relationship between heavy alcohol consumption and subarachnoid hemorrhage has also been reported. Although the question of direct effects of alcohol on the cerebral circulation requires further study, variables of cigarette smoking and hypertension are likely contributing factors. It remains possible that alcohol has a direct effect on risk factors for ischemic cerebral infarction and subarachnoid hemorrhage.[6]

Unfortunately, very little is known about the extent of alcohol-related cognitive decrements in the general population or the thresholds for these effects. The availability of computed tomographic (CT) brain scanning and more sophisticated neuropsychometric testing provides new methods to study the problem. Few studies to date adequately control for alcohol consumption, nutritional state or the use of other drugs and they often lack precise methods of assuring abstinence. Even clinically unimpaired drinkers during detoxification may have neuropsychological and CT abnormalities.[7-10] Especially difficult is the quantitative assessment of alcohol's effect in predicting cortical atrophy or cognitive dysfunction. This has made it almost impossible to precisely define the lower limits of these effects. Even if studies of clinically unimpaired persons who consume large amounts of alcohol are carefully controlled for age, there may be subtle differences in CT scanning or neuropsychological testing. Because it is equally difficult to control for nutritional variables and neuropsychological measurements before any alcohol consumption, it is not yet possible to quantitate the lowest dose of alcohol required to injure the nervous system. The evidence for reversibility of CT abnormalities requires further study. Reliable, inexpensive neuropsychological indicators to follow reversibility are needed.

This new information raises important questions of whether or not there are CT abnormalities or neuropsychological deficits that precede the onset of alcohol abuse. Tarter and associates[11] studied neuropsychological deficits in children who are at risk for alcohol abuse. The problems of control variables and bias are immense. By investigating two groups of adolescents who differed only on the basis of the presence or absence of paternal alcohol consumption, suggestive data are presented that neuropsychological impairments that may have been considered to be a consequence of alcohol use may, in some instances, have actually preceded alcohol consumption.[11] Thus, prospective studies of persons at risk is the best research paradigm for answering the threshold question of alcohol toxicity to the nervous system.

Populations at Risk

Alcohol and many other drugs cross the placenta and affect the fetus. What is the threshold for the effect on a fetus? A common pattern of birth defects and mental retardation among some children of women consuming large amounts of alcohol raises serious concern and has prompted intensive research into the relationship between alcohol consumption and pregnancy. French investigators and independent US investigators have identified specific malformations that have been labeled the fetal alcohol syndrome. Children of women who drink heavily may not have all the manifestations of this syndrome but may present with only lowered birth weight or learning deficits. Data on miscarriages, stillbirths and abortions have posed immense scientific difficulties in affirming the dose-response relationships of alcohol consumption and fetal injury. Control of smoking, diet, other drugs and occupational exposures currently frustrates investigators. Most studies to date in animals and humans strongly suggest that alcohol is teratogenic and embryotoxic.[3]

Quellette and colleagues[12] studied heavy drinkers defined as consuming an average of more than 45 ml of absolute alcohol per day, with five or more drinks on at least one occasion per month. After delivery, a detailed evaluation showed that twice as many infants born to heavily drinking mothers were abnormal compared with infants born to either moderately drinking or rarely drinking women. In another study, the offspring of women who consumed 39 ml or more of absolute alcohol per day just before or during pregnancy were compared with those of light drinkers or women who abstained.[13] The evaluations, conducted without prior knowledge of maternal consumption, showed clinical features of abnormal growth and morphogenesis in babies born to heavy drinkers. Other studies attempting to control for smoking have shown that two to six drinking sessions per week at levels as low as 30 ml of absolute alcohol per session or even as low as 15 to 30 ml per day alter the risk of spontaneous abortion.[14]

Other effects during pregnancy, such as the direct pharmacologic effect of alcohol on infant vital function or consumption of alcohol during lactation, require further study. What has emerged from this information is an apparent correlation between maternal alcohol consumption and a risk of fetal abnormalities. Although it has been difficult to control for all variables, drinking alcohol does place a pregnancy at risk; no safe level of maternal alcohol consumption during pregnancy has been defined. Studies of paternal alcohol use in animals and humans and the effect on fetal outcome are also as yet inconclusive.[15]

Of special note is that the desire to have a healthy baby is a powerful motivating force in modifying alcohol consumption. Examination of cohorts of newborns suggests the benefits to offspring when drinking ceases before the third trimester.[16] There may be a critical period in the early weeks after conception when many women are unaware that they are pregnant in which alcohol could pose special problems. Because the lowest threshold of effects has not been defined, some have advocated that if a woman is planning to become pregnant she should give up alcohol altogether or limit herself to less than one drink per day.[17,18]

Pregnant women may be only one of the groups at risk for alcohol effects. Studies of special ethnic groups in which the rate of alcohol metabolism is examined yield statistically significant differences, but there have been few clinical correlates to establish the importance of these metabolic differences. Immediate or prolonged changes of tolerance may also vary with race but, generally, studies in this area have not provided information to allow reliable predictors of populations at risk. It has been suggested that physicians are more vulnerable to alcohol and drug dependency than the general population. Drug use and abuse of prescription drugs may also be more prevalent among physicians, although this is difficult to study, as physicians may come to attention at a higher rate than nonphysicians. Close monitoring of physicians may, in part, account for the better prognosis that is alleged for physicians with alcohol and drug-dependency

problems.[19] Special alcohol problems among seamen, priests and military personnel have also been suggested. Similar difficulties have also been reported for unemployed persons or for those who work changing schedules.[20] Occupational variables are so difficult to control for that all of these studies require more precise methods.

Alcohol and Cancer

The clinical recognition that cancer of the mouth, pharynx, larynx, esophagus and liver appears to have a relationship to alcohol consumption has initiated research into the possible role that alcohol might play in carcinogenesis. In case-control studies an increased incidence of selected types of cancer has been found in a number of different populations throughout the world and these have been related to alcohol consumption. Although the mechanism for this effect is unknown, there have been attempts to control other variables such as smoking, nutrition and hygiene. Because the mechanism by which alcohol might increase the risk of cancer is unknown, it has been difficult in case-control methods to consider all the variables. Pollack and colleagues[21] conducted a prospective cohort study of the relationship between alcohol consumption and the subsequent occurrence of epithelial cancer at five specific sites to determine the impact of alcohol when carefully controlled for age, cigarette smoking and type of alcoholic beverage. The authors found a positive association between monthly alcohol consumption in the range of 15 liters (500 oz) and an increased risk of rectal cancer in Japanese men in Hawaii.

Although the methodologic problems in this type of research are evident, the consistency of findings is impressive. Much more information is required before a threshold level of alcohol consumption as it relates to cancer can be established.[21,22] Alcohol itself does not appear to be a carcinogen in most systems tested, but it is a good solvent for other chemicals and may carry potential carcinogens produced in fermentation or processing.

Gastrointestinal Effects

Alcohol can injure the esophagus, stomach, small intestine, pancreas and liver. Short- and long-term alcohol consumption results in direct injury to the mucosa of the upper gastrointestinal tract. The mechanism of this injury and the dose of alcohol required are unclear. Even small doses of alcohol can directly or indirectly stimulate acid secretion or cause alteration of the mucous protective barrier of the upper gastrointestinal tract. Oral and intravenous administration of alcohol, even in relatively small doses, may cause alterations in gastrointestinal motility and alter absorption of essential nutrients.[3] Alcohol increases pancreatic secretion and may cause obstruction to pancreatic secretions, resulting in increased pancreatic pressure and extravasation of pancreatic secretions into interstitial tissues, thus injuring the pancreas.

Bjarnason and co-workers[23] studied intestinal permeability with sodium chromate[51] Cr-labeled ethylenediaminetetraacetic acid in nonintoxicated patients who had alcoholism but without cirrhosis or overt clinical manifestations of malabsorption or malnutrition. These patients consumed about five to ten drinks of alcohol per day for three years and showed an increase in intestinal permeability to compounds with a molecular weight less than 5,000. Although this method does not indicate the exact site of the altered permeability, the overall abnormalities of absorption suggest that even in the absence of obvious malabsorption, increased permeability could accelerate intestinal damage by the loss of essential nutrients. Unfortunately, it is not known at this time whether lower doses of alcohol will also cause this abnormality of gastrointestinal absorption.

Even though persons who drink alcohol regularly may apparently consume a normal number of calories, they are malnourished by the standards of appropriate laboratory tests. One gram of alcohol supplies 7.1 calories and a liter of spirits produces about 3,300 calories. Because alcohol cannot be stored, it must be metabolized and the calories derived make no contribution to the energy of nutrition but may contribute to obesity. There are many reasons, in addition to the intestinal leak described, why persons with chronic alcoholism might become malnourished. These reasons have been fully reviewed recently by Sherlock.[24] Obviously, there can be end-organ damage to the upper gastrointestinal tract, pancreas or liver. Alcohol causes alterations of protein synthesis and amino acid metabolism and may alter important immune mechanisms, mineral and electrolyte balances and vitamin absorption and utilization. Unfortunately, the exact dose of alcohol that increases the minimum daily requirements of essential nutrients, or the exact dose that would cause end-organ damage, is not known. Until the basic mechanism for these toxicities is understood, a rational recommendation as to the minimum dose to ensure safety cannot be given.

Alcohol consumption is also associated with hyperuricemia and gout. With prolonged administration of alcohol to gouty patients with normal renal function, a mean peak blood alcohol concentration of only 13 mg per dl was shown to increase urate synthesis by enhancing the turnover of adenine nucleotides.[25] Higher blood concentrations of alcohol or lactate (or both) may alter urate clearances but only at much higher blood alcohol levels. Because hyperuricemia is recognized as a possible biochemical marker for alcohol ingestion and there is a higher incidence of gout among regular drinkers, these changes in nucleotide metabolism may have important consequences in identifying markers of alcohol intake as well as pathologic mechanisms.

The nutritional deficiencies of water-soluble vitamins and the threshold for their induction by alcohol are now recognized to be subtle. Although classic thiamine deficiency and Wernicke's encephalopathy resulting from thiamine deficiency are still prevalent, much more subtle nutritional deficiencies are likely to be present.

Recent studies conducted in humans and in animals show that prolonged consumption of alcohol even associated with an adequate diet may result in a striking lowering of hepatic fat-soluble vitamins, especially vitamin A. Even Mallory's bodies in the liver, long associated with excess alcohol consumption, are postulated to be lesions that may result from vitamin A deficiency.[26] Because large supplements of vitamin A are known to be hepatotoxic, much more must be learned concerning doses of alcohol and their effect on vitamin A. It is possible that the toxicity of vitamin A is not due to vitamin A itself but rather to one of its metabolites because the theoretical beneficial effect of vitamin A supplementation falls within a very narrow range. Many more studies are required

before therapeutic recommendations for vitamin A replacement therapy are justified.[26,27]

The liver is one of the key organs of metabolism of alcohol and is relatively easily deranged with prolonged consumption. Because the mechanism by which alcohol causes fatty liver, alcoholic hepatitis or cirrhosis is not currently known, it is difficult to estimate the total dose required to produce these pathologic changes. Suggestions from France are that as little as 60 grams a day (about six drinks) will suffice to cause liver dysfunction in men and as little as 20 grams a day (about two drinks) in women.[28] Acetaldehyde and superoxide anion have been suggested to be mediators for the more advanced features of alcohol-induced liver dysfunction.[29] Because the liver is so essential in the detoxification of many substances, it is also theoretically possible that alcohol alters basic liver function and that other toxic agents are the primary cause of the liver disease. Immunologic abnormalities have also recently been described to account for alcohol-induced liver disease.[30] Of special note are sex-related differences in cases of alcohol-induced liver disease.[31,32] Changes induced by estrogens or alterations of peak blood concentrations of alcohol in women have suggested—but do not prove—the observed sex differences in the susceptibility to alcohol-induced liver damage. Nonetheless, these pose important indices that must be added to any assessment of risk for alcohol consumption.

It has been suggested that persons who are symptomless carriers of the hepatitis B surface antigen (HBsAg) are at risk for alcohol-induced liver abnormalities. An amount of alcohol that is harmless to HBsAg-negative subjects, 80 grams (about eight glasses) of wine appears to enhance liver damage.[33] Unfortunately, there were not enough women in the study to test the susceptibility of the hepatotoxic effects of alcohol in HBsAg-positive female carriers.

Cardiovascular Effects

Alcohol administration alters the cardiovascular system in many ways. Direct injury to the myocardium from alcohol or one of its metabolites was initially thought to be due to thiamine deficiency or contaminants in alcoholic beverages. Alcohol cardiomyopathy is now thought to occur in men with heavy drinking episodes over a prolonged period and is not solely due to thiamine deficiency. Arrhythmias associated with social drinking or alcohol withdrawal have also been described in studies, such effects being labeled "holiday heart."[34,35] After the administration of 90 ml of 80-proof alcohol, significant atrial or ventricular arrhythmias developed in 10 of 14 patients. It is possible that these changes are due to direct effects of alcohol or to alterations of electrolyte balance.

Alcohol use is also apparently linearly related to systolic and diastolic blood pressure independent of adiposity, salt intake, coffee drinking or cigarette smoking.[36,37] Although magnesium deficiency has also been associated with changes in blood pressure and alcohol intake, convincing data are not yet available to link these two observations. Current data do not show the threshold of alcohol administration that causes alterations in electrolyte balance. The alcohol-related increase in blood pressure is likely an important clinical factor when diagnosing and treating hypertension.

The incidence of coronary heart disease has been suggested to be lower in persons consuming less than three drinks per day when compared with persons who totally abstain from alcohol. The notion that small amounts of alcohol consumption might be protective to the cardiovascular system emerged from evidence suggesting that elevated levels of circulating high-density lipoprotein (HDL) occur with alcohol consumption. However, more recent studies note that HDL is a heterogeneous group of lipoproteins with at least two major subclasses.[38,39] The less dense HDL_2 is epidemiologically associated with reduction of heart disease risk and the more dense HDL_3 is not clearly related to heart disease. Exercise and estrogens increase HDL_2, not HDL_3. Haskel and colleagues[38] showed that administration of one to three drinks of alcohol per day raised levels of HDL_3 but not HDL_2. When this quantity of alcohol was stopped, levels of HDL_3, not HDL_2, decreased. The complexity of these observations has been summarized by Lieber.[39] Epidemiologic studies do suggest, when carefully controlled, that modest alcohol intake is associated with a decreased incidence of coronary heart disease and with increased levels of HDL_3, rather than HDL_2. In the absence of severe liver disease, high alcohol intake results in high levels of HDL_2, but there is no evidence of protection against coronary heart disease. When alcohol use is associated with severe liver disease, HDL fractions decrease. The clinical significance of this information is not fully appreciated as yet.

Endocrine Effects

In the past ten years a substantial amount of literature has been produced on the effect of alcohol on the endocrine system.[40] Sex-related differences in the hypothalamic pituitary gonadal axis, alterations of steroidogenic enzymes and altered hormone binding have all been described. Symptoms of altered endocrine function, especially in men with liver disease, are well known. Gynecomastia, loss of hair, testicular atrophy and spider angiomata may be effects of alcoholic or liver disease or both. Whether these changes occur without liver dysfunction is an unresolved question that requires further study.

Alcohol and Aging

West and associates have reviewed the significant medical, psychiatric and social implications of alcohol consumption in the elderly.[1] Alcohol use is the second leading cause of admission of elderly persons to psychiatric institutions. Elderly persons do have altered pharmacokinetics for alcohol; the volume of distribution of alcohol is lower in the elderly, yet plasma clearance rates are unchanged. In addition, older persons seem to have greater brain sensitivity to alcohol than younger. Pharmacokinetic factors do not account for the greater vulnerability of normal elderly persons to alcohol. Although it is claimed that small amounts of alcohol may be useful therapeutically for elderly persons, current information does not tell us the threshold for safety in aging patients.

Alcohol Chemical-Drug Interactions

Many studies have shown the important pharmacologic and therapeutic interactions of alcohol with many drugs and chemicals. Alcohol may occasionally antagonize other drug effects, but most often it is additive or superadditive. Because it is a potent enzyme inducer, alcohol may appear to antago-

nize the effects of other agents until abnormalities of liver function occur.

Commonly, alcohol acts directly as a sedative hypnotic agent working at a similar site of action with other sedative hypnotic agents. Alcohol may indirectly alter absorption, distribution, excretion or metabolism of other agents. Potentially serious interactions between alcohol and chemical agents in the workplace exist. Amides, oximes, thiurams and carbamates are all known to inhibit the enzyme aldehyde dehydrogenase.[41] These agents produce symptoms similar to those seen with elevated acetaldehyde levels that result after disulfiram (Antabuse) is mixed with alcohol. Alcohol is also known to enhance the toxicity of many halogenated hydrocarbons, especially carbon tetrachloride and trichloroethylene. Because even small amounts of alcohol can cause these interactions, workplace exposures must be added to the risk analysis of alcohol use.

An especially important type of alcohol interaction occurs with over-the-counter products, particularly aspirin. Ingesting less than 50 grams (about five drinks) of alcohol prolongs the bleeding time of normal subjects receiving as little as 325 mg of aspirin.[42] Alcohol has no demonstrable effect on bleeding time. When aspirin and alcohol are mixed, there will be pronounced prolongation of bleeding for at least 36 hours.[42] One must be careful to weigh this type of interaction when making an overall health risk assessment. A 50-gram dose of alcohol (approximately five drinks) is associated with the alcohol concentrations that are often achieved in social settings.

Drug Abuse

Inhalants, hallucinogens, cocaine, abuse of prescription psychotherapeutic agents and marijuana are the most widely used nontherapeutic psychoactive drugs. Emergency management of intoxication, overdose and withdrawal syndromes is now widely recognized as a common continuing medical problem.[43] Nicholi[44] has reviewed the current widespread use of nontherapeutic psychoactive agents, which he calls a "modern epidemic." Drug abuse survey data presented in many studies are limited because of lack of supporting toxicology laboratory data, poor documentation for drug interactions, lack of quantitative dose estimations and confounding variables of socioeconomic status. Because alcohol is the common background for much of the nontherapeutic use of psychoactive agents, the entire field should be described more appropriately as polydrug abuse. Whether these agents are used for pleasure seeking or for release of discomfort or out of curiosity has never been fully quantitated. The major issue to consider is whether medical sequelae can result from the use of these agents in doses small enough not to impair performance.

There is clear evidence that inhaling glues, coolants, paint thinners, nail polish, gasoline and nitrates can cause major acute and chronic medical consequences. In addition, the use of hallucinogenic agents such as phencyclidine hydrochloride, even in low doses, can be associated with severe medical consequences. Cocaine abuse is apparently spreading throughout the United States. An increase in cocaine "free-base" smoking is likely to increase the number of cocaine users needing medical attention.[45] "Free base" is made by extracting cocaine hydrochloride with alkali; the residue, unlike the hydrochloride, is volatile and not degraded by smoke or heat. Nonpsychiatric complications of chronic cocaine use depend on the route of administration. Nasal septal necrosis with intranasal use, lung damage in smokers and life-threatening infection from intravenous injection[45] can all occur.

Abuse of sedatives or stimulants with or without medical prescriptions is a well-known problem. Because of the difficulty of quantitating the nature of the problem and estimating the total dose delivered, scientists are left with attempts to quantify doses that produce psychological dependency, tolerance and withdrawal.

Based on questionnaire information, marijuana is considered to be the most widely used illicit drug. The health effects of prolonged marijuana use have been extensively reviewed.[44] There is a suggestion that the regular use of marijuana is associated with the use of other psychoactive agents. If parents smoke, drink or use psychoactive agents, their offspring will generally be more prone to use illicit drugs.[44] This area is very complex and is often complicated by a background of alcohol use; there is little scientific evidence to assure that the regular use of nontherapeutic psychoactive agents can in any way be described as safe.

Summary

The analysis of low-dose effects of alcohol and nontherapeutic psychoactive drugs is bewilderingly complicated because we do not know the basic mechanism of injury for these agents. Clinical diagnostic tests are often imprecise in separating tissue effect from tissue pathology. The risk assessment of low doses of these agents has inherent limitations. Basic weaknesses in epidemiology, animal extrapolations and interactions heighten the difficulty. What risk is "acceptable" to the individual or society? Freedom of individual choice may conflict with public policy. There is also the reality of the impossibility of complete removal of risk.

Unfortunately, risk assessment must proceed with incomplete information if we are to give rational personal health promotion recommendations.[46] This poses an enlightened challenge that must be addressed with insufficient information. Given the information at hand the following are reasonable suggestions for personal health maintenance:

- Illicit recreational drug use of inhalants, hallucinogens, stimulants, narcotics and sedative hypnotic drugs poses an unacceptable risk.
- Groups at special risk, such as persons who have been alcohol or drug abusers, pregnant patients, elderly persons or patients taking other medications including aspirin should not ingest alcohol or other medications unless they are under medical supervision.
- The threshold for increased mortality from "regular" use of alcohol is three to five drinks; the risk rises sharply after six or more drinks per day. Cardiovascular mortality data concerning one to two drinks per day compared with total abstention suggest a favorable outcome, but further studies are required.
- Current advertising, availability and cost factors for alcohol require modification for optimal health maintenance. Insufficient financial resources are presently devoted to education, patient services and research.

Recognizing the shortcomings of the information base on which these recommendations are made, it is clear that with

insufficient dollars for health care, it will be necessary to redefine these recommendations for individuals and society as more is learned.

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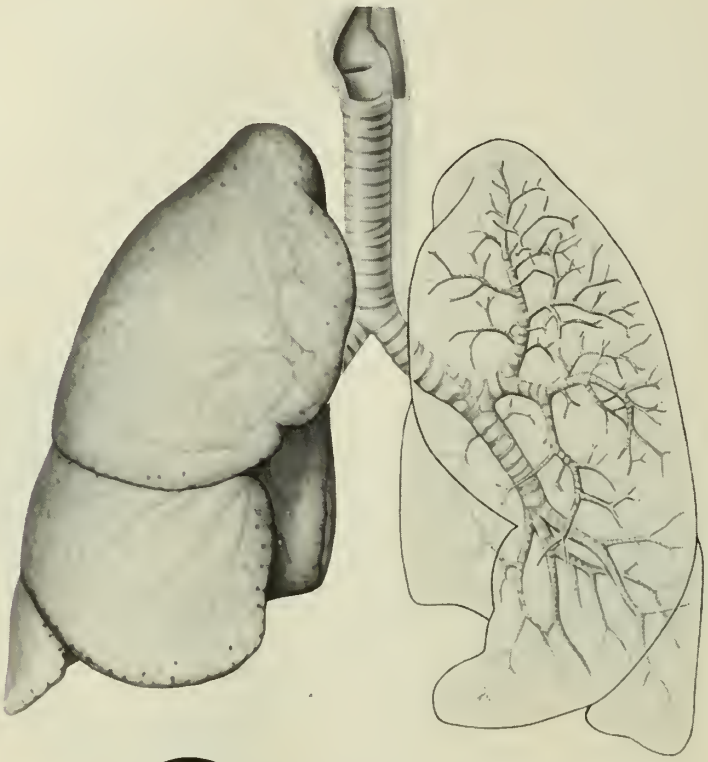

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Contraindication Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

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Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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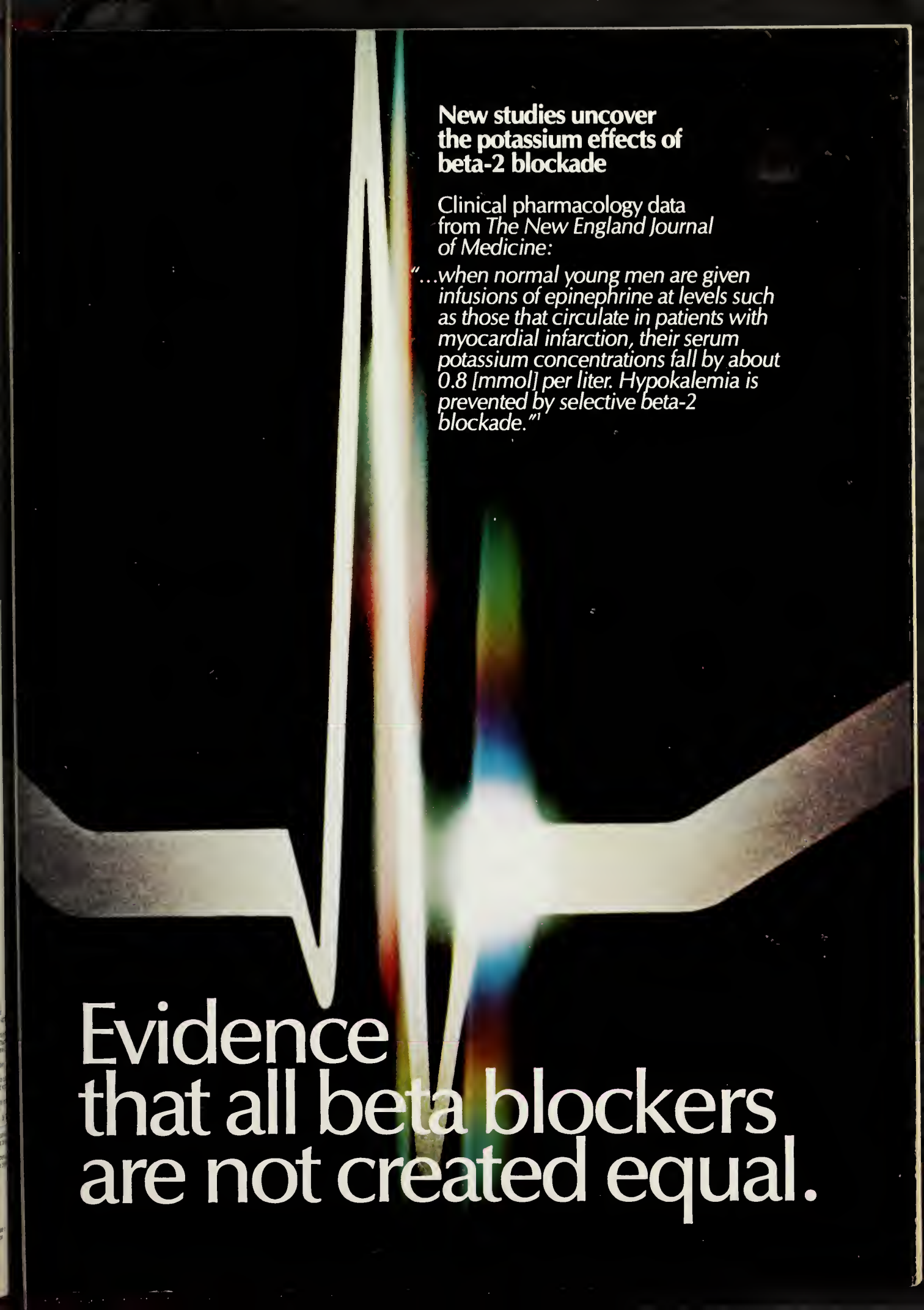

New studies uncover the potassium effects of beta-2 blockade

Clinical pharmacology data from *The New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."[1]

Evidence that all beta blockers are not created equal.

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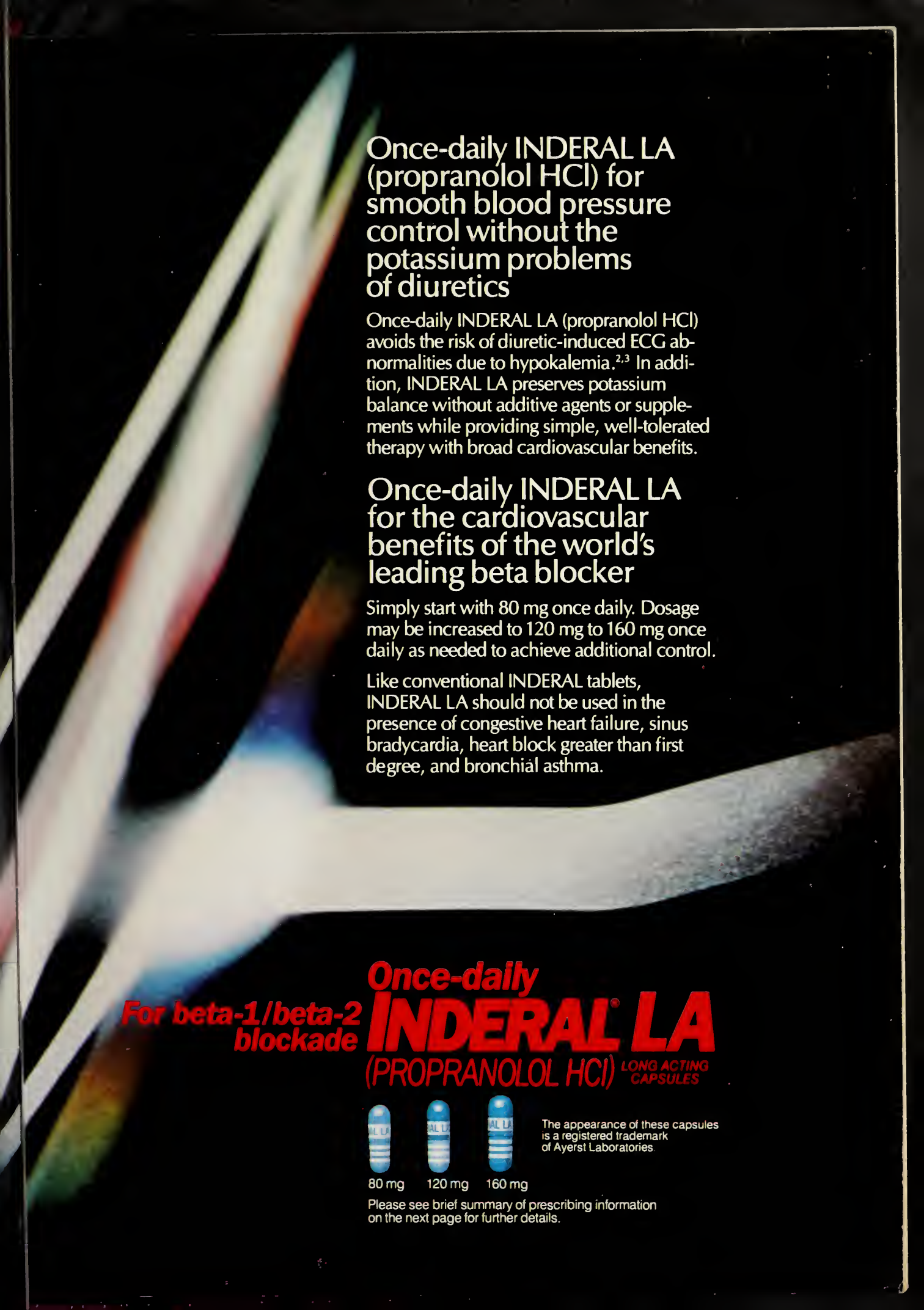

Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[2,3] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

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Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

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For beta-1/beta-2 blockade

Once-daily INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which after propranolol the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Epstein FH, Rosa RM. Adrenergic control of serum potassium. *N Engl J Med* 1983; 309:1450-1451. **2.** Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **3.** Holme I, Helgeland A, Hjermann I, et al. Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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(Continued from Page 766)

February 8-10—**5th Annual Current Concepts in Ophthalmology 1985.** UCSD at Hotel Del Coronado, San Diego. Friday-Saturday. 15 hrs. Contact: UCSD.

March 1-2—**14th Jules Stein Seminar: Retino Vitreal.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. 16 hrs. Contact: JSEI, UCLA School of Medicine, Los Angeles 90024. (213) 825-4617.

March 14-15—**Modern Surgical Techniques and Their Effects of the Cornea.** Pacific Medical Center at Clift Hotel, San Francisco. Thursday-Friday. Contact: Pacific Medical Center, Continuing Education, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

PATHOLOGY

February 3-6—**12th Annual Course in Genitourinary Pathology.** UCI at Memorial Medical Center, Long Beach. Sunday-Wednesday. 36 hrs. Contact: UCI.

February 16—**Oxygen Radicals, Pathology and Aging.** UCSD at Holiday Inn at the Embarcadero, San Diego. Saturday.

PEDIATRICS

January 25-26—**Advanced Fetal Heart Rate Monitoring Seminar.** UCI at South Coast Plaza Hotel, Costa Mesa. Friday-Sunday. 12 hrs. Contact; UCI.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 25-27.

February 2-9—**Pediatric Emergencies.** UCSD at Snowbird Resort, Utah. One week. 21 hrs. Fee: $315-$350. Contact: UCSD.

March 7-9—**Brain Insults in Infants and Children: Pathology, Evaluation, Diagnosis and Acute Management.** UCSD at Holiday Inn Embarcadero, San Diego. 17 hrs. Contact: UCSD.

PSYCHIATRY

January 27-February 1—**Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. Contact:UCD.

RADIOLOGY

February 27-March 1—**5th Annual Approaches: Radiologic, Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: UCSF.

March 6-9—**6th Annual Sierra Radiology Conference.** Sacramento Radiology Society at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday. 20 hrs. Contact: John P. Walter, PhD, MD, Program Director, Sacramento Radiology Research and Education Found., PO Box 19184, Sacramento 95819.

SPORTS MEDICINE

January 13-17—**Sports Medicine: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: UCD.

January 26—**Nutrition for Athletic Performance.** American Heart Association at University of California at Berkeley, Berkeley. Saturday. 4 hrs. Fee: $40. Contact: American Heart Association, PO Box 5157, Oakland 94605. (415) 632-9606.

March 18-22—**University of Hawaii Sports Medicine Course.** Ohio State University at Princess Kaiulani Hotel, Waikiki, HI. Monday-Friday. 18 hrs. Fee: $280. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu, HI 96822. (808) 948-8244.

SURGERY

January 11-12—**Laser for the Plastic Surgeon.** Plastic Surgery Educational Foundation at Ralph K. Davies Medical Center, San Francisco. Friday-Saturday. 7 hrs. Contact: PSEF, Michigan Avenue National Bank, PO Box 94452, Chicago, IL 60690.

January 14-18—**Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. $1,200.

January 18-19—**Surgical Superbowl.** Santa Clara County Surgical Society at Hyatt San Jose. Friday-Saturday. 16 hrs. Contact: Richard Hardy, MD, 2505 Samaritan Dr. #302, San Jose 95124.

January 18-19—**7th Annual Postgraduate Course in Surgery.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday. Contact: UCD.

January 21-25—**8th Annual San Diego Postgraduate Assembly in Surgery.** UCSD. Monday-Friday. Contact: UCSD.

February 11-15—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

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December 31—**4th Annual Potpourri of Medicine Seminar.** Huntington Memorial Hospital, Pasadena. Monday. 6 hrs. $110. Contact: Med. Staff Coord., Huntington Memorial Hospital, 100 Congress St., Pasadena 91105. (818) 440-5165.

January 14-18—**Intensive Course in Geriatric Medicine.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Monday-Friday. 33.75 hrs. Fee: $410.

January 17-19—**Physician & Hospital Conference.** USC at Hyatt Del Monte, Monterey. Thursday-Friday.

January 20-23—**54th Annual Midwinter Clinical Conference.** Research Study Club of Los Angeles at Los Angeles Hilton Hotel. Sunday-Wednesday. 24 hrs. Contact: Louise Ball, Executive Secretary, PO Box 1464, South Pasadena 91030.

January 23-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** Sir Francis Drake Hotel, San Francisco. Wednesday-Saturday.

January 25-26—**Physical and Occupational Therapy Program.** UCD at Beverly Garland, Sacramento. Friday-Saturday.

January 25-27—**Practical Dermatology & Dermatologic Office Procedures for Primary Care Physicians.** UCSD at Vacation Village Resort, San Diego. Friday-Sunday. 20 hrs. Fee: $325.

January 31-February 2—**Recent Advances in Geriatric Medicine: Dementia in the Elderly.** UCSD at Holiday Inn at the Embarcadero, San Diego. Thursday-Saturday. 13 hrs. $210.

February 1-3—**Primary Care Update: A Practical Approach.** Scripps Clinic and Research Foundation at Vacation Village Resort, San Diego. Friday-Sunday. 14 hrs. Contact: Dianne Tisue, Scripps Clinic, 10666 North Torrey Pines Rd., La Jolla 92037.

February 6-8—**Neurology for Non-Neurologists.** UCSD at Holiday Inn at the Embarcadero, San Diego. Wednesday-Friday. 21 hrs. Contact: UCSD.

February 11-16—**UCI Family Practice Refresher**

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February 11-22—**Intensive Residency on Occupational Medicine.** UCSF at San Francisco. Two weeks. 80 hrs. Fee: $1,000. Contact: UCSF.

February 13-15—**Clinical Laboratory Molecular Analysis: Future Direction.** Scripps Clinic and Research Foundation at Vacation Village San Diego. 21 hrs. Contact: Dianne Tisue, Scripps Clinic, 10666 North Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

February 22-23—**American College of Physicians: 1985 Regional Scientific CME Meeting.** ACP at Doubletree Inn, Monterey. Friday-Saturday. Contact: Jerry P. Lewis, MD, 618 Francisco Place, Davis 95616.

February 23-24—**Expanding Horizons.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF.

February 28-March 2—**California Medical Association Postgraduate Institute.** Curry Village, Yosemite. Thursday-Saturday. Contact: CMA, 44 Gough St., San Francisco 94103-1233.

March 1—**11th Annual Diabetes Program.** UCD. Friday.

March 6-8—**35th Annual Course for Physicians in Family Practice.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin Jackson, Office of Continuing Education, PO Box 7921, San Francisco 94115. (415) 885-7269.

March 7-10—**Dermatologic Survey: State of the Art.** UCSF at Incline Village, Nevada. Thursday-Sunday. Fee: $400.

March 8-13—**California Medical Association Annual Session** at Town and Country Hotel, San Diego. Friday-Wednesday. Contact: Barbara Smart, CMA, 44 Gough St., San Francisco 94103-1233. (415) 863-5522, ext. 404.

March 10-13—**New Strategies for Common Clinical Problems.** UCSF at Granlibakken Ski and Raquet Resort, Tahoe City. Sunday-Wednesday.

March 13-17—**Orthopaedic Symposium.** UCD at Silverado Country Club, Napa. Wednesday-Sunday.

March 25-29—**Family Practice Refresher Course—1985.** UCSD at Palm Springs Spa Hotel. Monday-Friday. 30 hrs.

March 29-31—**Office Emergencies in Primary Care.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

IDAHO

February 16-23—**Internal Medicine.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 17-22—**11th Stanford-Palo Alto Medical Foundation Research Institute Winter Course in Infectious Diseases.** Sun Valley. Sunday-Friday. Contact: Registrar, American College of Physicians, 4200 Pine St., Philadelphia, PA 19104.

February 23-March 2—**Office Orthopaedics.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 2-9—**Electromyography.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

February 20-23—**Big Sky Pulmonary/Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Wednesday-Saturday. Contact: ALA of Montana, 825 Helena Ave., Helena 59601. (406) 442-6556.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 12-13—**3rd Annual Albuquerque Family Practice Seminar—Medical Issues in Gerontology.** Albuquerque. Saturday-Sunday. Marriott Hotel. 13 hrs. AMA Cat. I, AAFP Prescribed. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

January 18-19—**Carrie Tingley Hospital 15th Winter Orthopaedic Seminar.** Albuquerque. 10 hrs. AMA Cat. I. Friday-Saturday. Hilton Inn. Contact: Office of Medical Affairs, Carrie Tingley Hospital, PO Box 25447, Albuquerque 87125. (505) 841-9121.

January 23-27—**New Mexico Metabolism Symposium.** Taos. Wednesday-Sunday. Tennis Ranch. 12 hrs. AMA Cat. I. Contact: Office of CME, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87106. (505) 262-7353.

February 1-3—**Advances in Internal Medicine V.** Albuquerque. Friday-Sunday. 15 hrs. AMA Cat. I. Veterans Administration Medical Center. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

February 4-8—**Alta Medical Conference.** Alta, Utah. Monday-Friday. 10 hrs. AMA Cat. I. Contact: New Mexico Mid-Winter Study Group, 717 Encino Pl. NE, #9, Albuquerque 87102. (505) 842-6762.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

February 15-16—**Heal Thyself—A Seminar Focusing on Quality of Life and Caring for Others.** Albuquerque. Friday-Saturday. Clarion Four Seasons. 11 hrs. AMA Cat. I. Contact: Office of CME, Presbyterian Hospital, Albuquerque 87102. (505) 841-1225.

February 21-23—**18th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

March 15-16—**Primary Care Orthopaedics.** Albuquerque. Friday-Saturday. AMFAC Hotel. 15 hrs.

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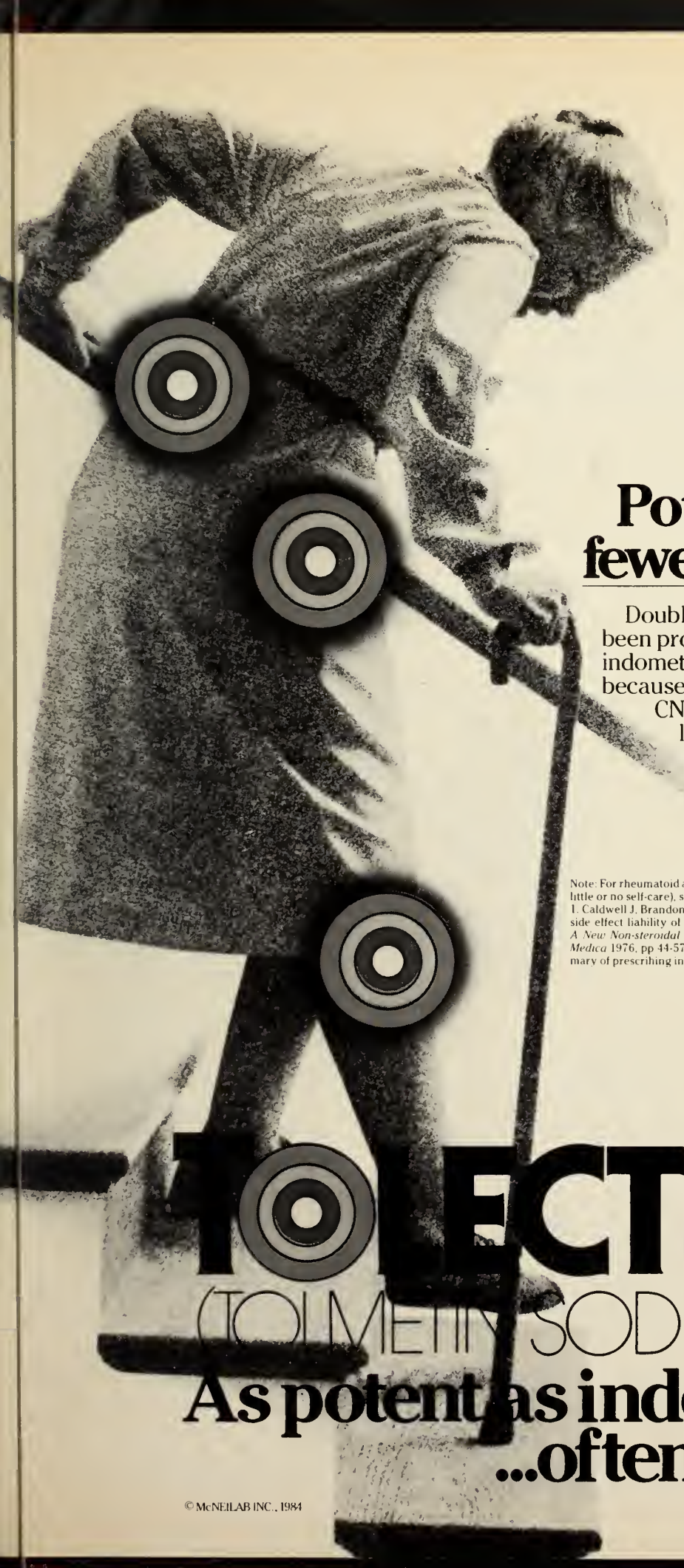

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1. Caldwell J, Brandon ML, Franz KH, et al: A double-blind comparison of the efficacy and side effect liability of tolmetin and indomethacin. Presented at a symposium: *Tolmetin A New Non-steroidal Anti-inflammatory Agent*. Washington, DC, April 1975, *Excerpta Medica* 1976, pp 44-57. See warnings, precautions, and side effects sections in brief summary of prescribing information on next page.

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SUMMARY OF PRESCRIBING INFORMATION
TOLECTIN® DS (tolmetin sodium)
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Contraindicated: In patients who have previously exhibited intolerance to it, patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria
Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. If TOLECTIN must be given to patients with active peptic ulcer, closely supervise for signs of ulcer perforations or severe gastrointestinal bleeding.
Precautions: *General*—Ophthalmologic examinations should be carried out within a reasonable time after starting chronic therapy and at periodic intervals thereafter.
Renal failure, sometimes acutely, associated with nephrotic syndrome has been reported. Closely monitor patients with impaired renal function, they may require lower doses.
TOLECTIN prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when TOLECTIN is administered.
In patients receiving concomitant TOLECTIN-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.
TOLECTIN should be used with caution in patients with compromised cardiac function.
The metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint (e.g., sulfosalicylic acid). No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.
As with other nonsteroidal anti-inflammatory drugs, anaphylactoid reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships which exist among nonsteroidal anti-inflammatory drugs, anaphylactoid reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds, particularly zomepirac sodium. Patients who have had anaphylactoid reactions on TOLECTIN should be treated with conventional therapy, such as epinephrine, antihistamines, and/or steroids.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with TOLECTIN. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue TOLECTIN.
Usage in Pregnancy—Because TOLECTIN has not been studied in pregnant women, use during pregnancy is not recommended.
Nursing Mothers—Because TOLECTIN may be secreted in human milk, nursing should not be undertaken while a patient is on this drug.
Drug Interactions—There have been rare reports that prothrombin time may increase and bleeding may occur.
Adverse Reactions: *Incidence Greater Than 1%*—The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.
Gastrointestinal: Nausea (11%), dyspepsia*, gastrointestinal distress*, abdominal pain*, diarrhea*, flatulence*, vomiting*, constipation, gastritis, and peptic ulcer.
Body as a Whole: Headache*, asthenia*, chest pain.
Cardiovascular: Elevated blood pressure*, edema*.
Central Nervous System: Dizziness*, drowsiness, depression.
Metabolic/Nutritional: Weight gain*, weight loss*.
Dermatologic: Skin irritation.
Special Senses: Tinnitus, visual disturbance.
Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred.
Urogenital: Elevated BUN, urinary tract infection.
*Reactions occurring in 3% to 9% of patients treated with TOLECTIN. Reactions occurring in fewer than 3% of the patients are unmarked.
Incidence Less Than 1% (Causal Relationship Probable)—*Gastrointestinal*: Gastrointestinal bleeding with or without evidence of peptic ulcer, glossitis, stomatitis, hepatitis, liver function abnormalities.
Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy.
Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis.
Cardiovascular: Congestive heart failure in patients with marginal cardiac function.
Dermatologic: Urticaria, purpura, erythema multiforme.
Urogenital: Hematuria, proteinuria, dysuria, renal failure.
Incidence Less Than 1% (Causal Relationship Unknown)—*Body as a Whole*: Epistaxis.
Full directions for use should be read before administering or prescribing.
For information on symptoms and treatment of overdosage, see full prescribing information.
Also available: TOLECTIN® (tolmetin sodium) tablets 200 mg, 100's—Military 6505-01-038-7460, VA 6505-01-038-7460A. Capsules 400 mg, 100's—VA 6505-01-091-9624A.
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(Continued from Page 912)

AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

April 11-13—**Seventh Annual Pediatric Cardio-Pulmonary Update.** Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

(Continued on Page 917)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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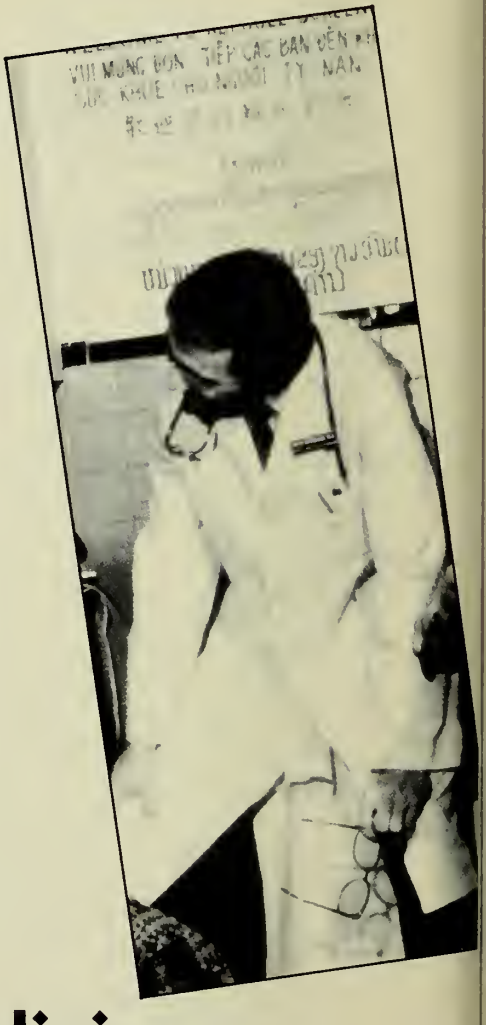

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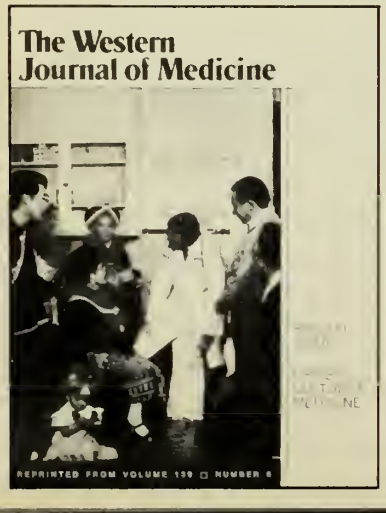

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(Continued from Page 915)

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

DERMATOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CMA.

FAMILY PRACTICE

February 11-15—**Family Practice Review Program.** Portland. Monday-Tuesday. Marriott Hotel. Contact: OHSU-CME.

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

PATHOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

SURGERY

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

February 10—**Alcohol and Drug Symposium.** Portland. Sunday. Marriott Hotel. Contact: OHSU-CME.

February 28-March 3—**Update in Rheumatology—1985.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

(Continued on Page 920)

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(Continued from Page 902)

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TACOMA: PHYSICIAN OPENING: Prefer Board eligible or certified Family Practitioner, Emergency Physician, or Internist with interest in acute care for ambulatory/minor emergency center. Position is half to two-thirds time with excellent scheduling. Contact Roger Simms, MD, or Terry Kendrick, MD, at 5702 N. 26th St., Tacoma, WA 98407; Telephone (206) 759-6655.

OB/GYN, CARDIOLOGIST, ORTHOPEDIC SURGEON—San Joaquin County—Board eligible/certified, multi-specialty group. Salary negotiable, early partnership, fringe benefits, growth capability. One hour from San Francisco. Send résumé to Box 6455, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

UNIVERSITY OF CALIFORNIA, IRVINE, seeks ABFP certified family physician with extensive experience in pre-doctoral medical education in FP—in direction of FP residents and administration in University setting to lead a comprehensive education program for all levels of FP as Lecturer with security of employment. Send CV to Credentials Committee, Dept. of Family Medicine, UCI Med. Ctr., 101 City Dr. South, Orange, CA 92668. An Affirmative Action/Equal Opportunity Employer.

VIRGINIA MASON MEDICAL CENTER, SEATTLE, WA. Sports Medicine Physician wanted for rapidly growing department. Beautiful, new, 14,000 sq. ft. facility includes large offices and exam rooms, x-ray, physical therapy, Nautilus conditioning and aerobic exercise room. Present staff includes one orthopedic surgeon, one podiatrist and 3 physical therapists/athletic trainers. Position available immediately. Contact Don Labourr, Director, Mason Clinic Sports Medicine Center, 904 7th Ave., Seattle, WA 98104; Phone (206) 223-6487.

ENT: Third partner for active, established, practice—all aspects of ENT, in San Francisco Bay Area. Salary negotiable. Reply Box 6454, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

GENERAL SURGEON, Sun Valley/Ketchum, Idaho, with multi-specialty group to replace retiring surgeon. Send CV to Ivan Gustafson, MD, Box 2198, Ketchum, ID 83340; Phone (208) 726-9361

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GENERAL/FAMILY PRACTITIONERS. If you are looking for an opportunity to be in the forefront of medical care, practice preventive medicine, work with other innovative professionals, and earn a comfortable living in pleasant surroundings, send your curriculum vitae to Physician Placement Dept-49. An equal opportunity employer. CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

GENERAL SURGEON—Opening in a young dynamic growing consultative practice. This 130-physician, multi-specialty, prepaid group is located near Pacific Ocean beaches, Lake Tahoe ski areas, Stanford University and San Francisco. Cultural and educational activities abound. Please contact: Latimer Booth, MD, Chief, Department of Surgery, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119 or telephone collect (408) 972-6010.

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EVALUATION MEDICINE: Fast growing evaluation practice is establishing a new office in Orange County. Specialties sought are Board certified: Orthopedic Surgeon; Internist—Cardiologist, Pulmonary Specialist; Neurosurgeon; Psychiatrist; Otolaryngologist. This is an excellent opportunity for the practitioner who wishes to supplement his/her income or for the retired or semi-retired practitioner who wishes to work only part-time. This unique practice provides all management and support functions while allowing each physician complete flexibility in the scheduling of appointments. Please call or write Ms. Lisa Chew, Medical Evaluation Specialists, 1127 Wilshire Blvd., Suite 1209, Los Angeles, CA 90017 or call (213) 977-0540.

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SITUATIONS WANTED

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(Continued on Page 919)

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(Continued from Page 918)

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WESTERN WASHINGTON—Private practices available in OB/GYN, Pulmonary, Internal Medicine and Family Practice. For details, contact Eloise Gusman, 1 (800) 535-7698 or send CV to 2800 Veterans Blvd., Suite 170, Metairie, LA 70002. Our service is completely confidential and offered at no cost or obligation.

CALIFORNIA—Radiology, Ophthalmology, Ob/Gyn, Family, Internal, Surgery, Occupational Med., Pediatric, Orthopedic, Psychiatry, Dermatology, others. Contact; Mary Bradshaw, Practice Broker/Recruiter, 21 Altamount, Orinda, CA 94563, (415) 376-0762.

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(Continued from Page 917)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

February 9-16—**8th Annual Update in Clinical Microbiology/Immunology** (Sponsor: University of Utah). Saturday-Saturday. Park City. Fee to be announced. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 12-15—**14th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 28 hrs. Contact: Linda Twitchell, (801) 581-8633.

February 17-20—**26th Annual Ob/Gyn Update** (Sponsor: University of Utah). Sunday-Wednesday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 20-23—**Reproductive Endocrinology and Infertility** (Sponsor: University of Utah). Wednesday-Saturday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 22-26—**30th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. Fee to be announced. 16 hrs. Contact: Vicky Larsen, (801) 581-6115.

February 25-March 1—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 4-8—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 6-8—**Common Problems in Pediatrics VII** (Sponsor: University of Utah). Wednesday-Friday. Little America Hotel, Salt Lake City. Fee to be announced. 12 hrs. Contact: Wendy Ellis, (801) 363-1887 or Robert Bolte, MD, (801) 363-1221.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

March 12-22—**Transport Workshop: Neonatal-Maternal-Administration** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 69½ hrs. Contact: Anne Shanahan, (801) 581-2730.

March 18-22—**5th Annual Nutrition in Contemporary Medicine Symposium** (Sponsor: University of Utah). Monday-Friday. Park City. Fee to be announced. 29 hrs. Contact: M. Rita Thomas, MD, (801) 581-3581.

March 21-23—**Practical Neurology for Clinicians** (Sponsor: University of Utah). Thursday-Saturday. Sheraton Hotel, Salt Lake City. Fee to be announced. 18 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

December 18—**Fever of Unknown Origin.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

December 26-January 2—(HAWAII) **Medicine, Magic and Religion.** Maui. Wednesday-Wednesday. Royal Lahaina. Contact: U/W.

December 28—**Diagnosis of Sleep Disorders.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 4—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 11—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 11—**Treatable Hepato-Biliary Disease.** Seattle. Friday. Contact: VMMC.

January 15—**General Topics in Hematology.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 18—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 23-25—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

January 24-26—**Annual President's Meeting—Modern Ophthalmic Technology.** Washington State Academy of Ophthalmology at Seattle. Thursday-Saturday. Westin. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

January 25—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 30—**Controversies in Medicine Circuit.** Vancouver. Wednesday. Contact: U/W.

January 31—**Controversies in Medicine Circuit.** Olympia. Thursday. Contact: U/W.

January 31-February 1—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin. Contact: U/W.

February 1—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 8—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 16—**Interventional Radiology to Abdomen.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

February 16-23—(IDAHO) **Internal Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 19—**Total and Home Parenteral Nutrition.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

February 20-22—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

February 22—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

February 23-March 2—(IDAHO) **Office Orthopaedics.** Sun Valley. Saturday- Saturday. Elkhorn Resort. Contact: U/W.

March 1—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 2-9—(HAWAII) **Medicine in China.** Kauai. Saturday-Saturday. Royal Waikola. Contact: U/W.

March 2-9—(IDAHO) **Electromyography.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 9-16—(HAWAII) **Imaging for Non-Radiologists.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 19—**Epilepsy.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

March 22—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 23—**Magnetic Resonance Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

March 23-30—(HAWAII) **Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 28-29—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences. Contact: U/W.

March 29—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 30-April 6—(HAWAII) **Neurology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 5—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 11-12—**DRG.** Seattle. Thursday-Friday. Westin. Contact: U/W.

April 12—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 13—**Handicapped Infant.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

April 16—**Ballard Hospital Lectures.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 17-19—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

April 18-19—**Death Investigation.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

April 19—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

April 26—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 26-27—**Sexual Assault.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

May 2-3—**Exercising Women.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 3—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 10—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 15-17—**Infectious Diseases.** Seattle. Wednesday-Friday. Westin. Contact: U/W.

May 17—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 18—**Microcomputers in Rehab Medicine.** Seattle. Saturday. Contact: U/W.

May 21—**Ballard Hospital Lectures.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

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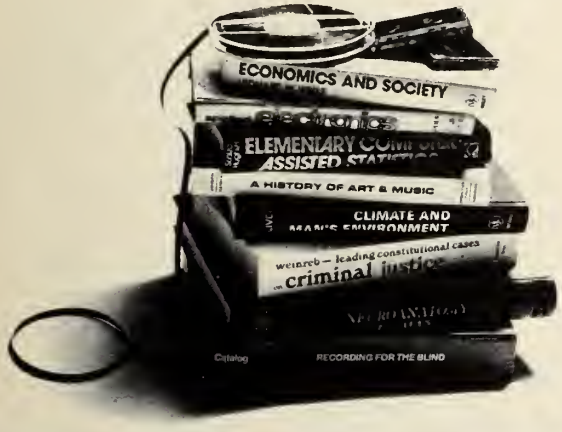

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May 22-24—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

May 30-31—**Mental Health Policy Forum.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

May 31—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 6-7—**Behavioral Medicine.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. Sheraton. Contact: U/W.

June 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Ballard Hospital Lectures.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 19-20—**Financial Planning for Physicians.** Victoria, BC. Wednesday-Friday. Empress Hotel. Contact: U/W.

June 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

WYOMING

January 25-26—**20th Annual Wyoming Medical Society Winter Seminar—Coronary Artery Disease Update—1985.** Holiday Inn, Cheyenne. Friday-Saturday. 10 hrs. Cat. 1. $50, WMS members; $100, nonmembers. Contact: Wyoming Medical Society, PO Box 4009, Cheyenne 82003. (307) 635-2424. WJM

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 8-11, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and County, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: 1985—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1985—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 433-4000. Annual Meeting: 1985—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: 1985—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1985—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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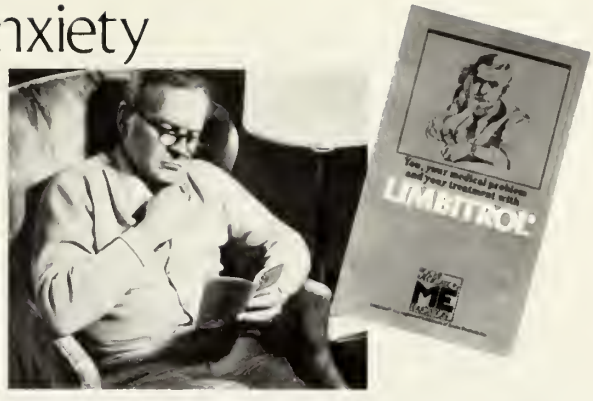
*Feighner JP: *Psychopharmacology* 61 217-225, Mar 22, 1979.



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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female; elevation and lowering of blood sugar levels; and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25: initial dosage of three or four tablets daily in divided doses; increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5: initial dosage of three or four tablets daily in divided doses; for patients who do not tolerate higher doses.
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)— bottles of 100 and 500. Tel-E-Dose® packages of 100. Prescription Paks of 50.

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Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Rapid clearing through dual action

Please see summary of product information on reverse side.

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